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Signed R. Mahoney

Dated 23 August 2004

6. AUG. 2003 15:16 ASTRAZENECA-PATENTS NO. 4291 P. 2

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P01/7700 0.00-0318423.1

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1. Your reference	101174	
2. Patent application number *(The Patent Office will fill in this part)*	0318423.1	6 AUG 2003
3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	AstraZeneca AB SE-151 85 Sodertalje Sweden	
Patents ADP number *(if you know it)*	7822448003	
If the applicant is a corporate body, give the country/state of its incorporation	Sweden	
4. Title of the invention	CHEMICAL COMPOUNDS	
5. Name of your agent *(if you have one)*	Tracy Burns	
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	AstraZeneca UK Limited Global Intellectual Property Mereside, Alderley Park Macclesfield Cheshire SK10 4TG	
Patents ADP number *(if you know it)*	7822471002	

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

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Continuation sheets of this form	
Description	70
Claim(s)	04
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Authorised Signatory Date 06/08/2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Jennifer C Bennett - 01625 230148

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Notes

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CHEMICAL COMPOUNDS

The present invention relates to quinazoline derivatives, processes for their preparation, pharmaceutical compositions containing them as active ingredient, methods for the treatment of disease states associated with angiogenesis and/or increased vascular permeability, to their use as medicaments and to their use in the manufacture of medicaments for use in the production of antiangiogenic and/or vascular permeability reducing effects in warm-blooded animals such as humans.

Normal angiogenesis plays an important role in a variety of processes including embryonic development, wound healing and several components of female reproductive function. Undesirable or pathological angiogenesis has been associated with disease states including diabetic retinopathy, psoriasis, cancer, rheumatoid arthritis, atheroma, Kaposi's sarcoma and haemangioma (Fan et al, 1995, Trends Pharmacol. Sci. 16: 57-66; Folkman, 1995, Nature Medicine 1: 27-31). Alteration of vascular permeability is thought to play a role in both normal and pathological physiological processes (Cullinan-Bove et al, 1993, Endocrinology 133: 829-837; Senger et al, 1993, Cancer and Metastasis Reviews, 12: 303-324). Several polypeptides with in vitro endothelial cell growth promoting activity have been identified including, acidic and basic fibroblast growth factors (aFGF & bFGF) and vascular endothelial growth factor (VEGF). By virtue of the restricted expression of its receptors, the growth factor activity of VEGF, in contrast to that of the FGFs, is relatively specific towards endothelial cells. Recent evidence indicates that VEGF is an important stimulator of both normal and pathological angiogenesis (Jakeman et al, 1993, Endocrinology, 133: 848-859; Kolch et al, 1995, Breast Cancer Research and Treatment, 36:139-155) and vascular permeability (Connolly et al, 1989, J. Biol. Chem. 264: 20017-20024). Antagonism of VEGF action by sequestration of VEGF with antibody can result in inhibition of tumour growth (Kim et al, 1993, Nature 362: 841-844). Basic FGF (bFGF) is a potent stimulator of angiogenesis (e.g. Hayek et al, 1987, Biochem. Biophys. Res. Commun. 147: 876-880) and raised levels of FGFs have been found in the serum (Fujimoto et al, 1991, Biochem. Biophys. Res. Commun. 180: 386-392) and urine (Nguyen et al, 1993, J. Natl. Cancer. Inst. 85: 241-242) of patients with cancer.

Receptor tyrosine kinases (RTKs) are important in the transmission of biochemical signals across the plasma membrane of cells. These transmembrane molecules characteristically consist of an extracellular ligand-binding domain connected through a segment in the plasma membrane to an intracellular tyrosine kinase domain. Binding of

ligand to the receptor results in stimulation of the receptor-associated tyrosine kinase activity which leads to phosphorylation of tyrosine residues on both the receptor and other intracellular molecules. These changes in tyrosine phosphorylation initiate a signalling cascade leading to a variety of cellular responses. To date, at least nineteen distinct RTK subfamilies, defined by amino acid sequence homology, have been identified. One of these subfamilies is presently comprised by the fms-like tyrosine kinase receptor, Flt-1, the kinase insert domain-containing receptor, KDR (also referred to as Flk-1), and another fms-like tyrosine kinase receptor, Flt-4. Two of these related RTKs, Flt-1 and KDR, have been shown to bind VEGF with high affinity (De Vries et al, 1992, Science 255: 989-991; Terman et al, 1992, Biochem. Biophys. Res. Comm. 1992, 187: 1579-1586). Binding of VEGF to these receptors expressed in heterologous cells has been associated with changes in the tyrosine phosphorylation status of cellular proteins and calcium fluxes.

The present invention is based on the discovery of compounds that inhibit the effects of VEGF, a property of value in the treatment of disease states associated with angiogenesis and/or increased vascular permeability such as cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, lymphoedema, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation including macular degeneration.

VEGF is a key stimulus for vasculogenesis and angiogenesis. This cytokine induces a vascular sprouting phenotype by inducing endothelial cell proliferation, protease expression and migration, and subsequent organisation of cells to form a capillary tube (Keck, P.J., Hauser, S.D., Krivi, G., Sanzo, K., Warren, T., Feder, J., and Connolly, D.T., Science (Washington DC), *246*: 1309-1312, 1989; Lamoreaux, W.J., Fitzgerald, M.E., Reiner, A., Hasty, K.A., and Charles, S.T., Microvasc. Res., *55*: 29-42, 1998; Pepper, M.S., Montesano, R., Mandroita, S.J., Orci, L. and Vassalli, J.D., Enzyme Protein, *49*: 138-162, 1996.). In addition, VEGF induces significant vascular permeability (Dvorak, H.F., Detmar, M., Claffey, K.P., Nagy, J.A., van de Water, L., and Senger, D.R., (Int. Arch. Allergy Immunol., *107*: 233-235, 1995; Bates, D.O., Heald, R.I., Curry, F.E. and Williams, B. J. Physiol. (Lond.), *533*: 263-272, 2001), promoting formation of a hyper-permeable, immature vascular network which is characteristic of pathological angiogenesis.

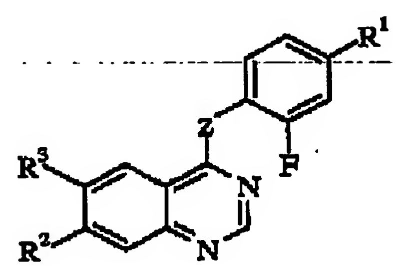
It has been shown that activation of KDR alone is sufficient to promote all of the major phenotypic responses to VEGF, including endothelial cell proliferation, migration, and

survival, and the induction of vascular permeability (Meyer, M., Clauss, M., Lepple-Wienhues, A., Waltenberger, J., Augustin, H.G., Ziche, M., Lanz, C., Büttner, M., Rziha, H-J., and Dehio, C., EMBO J., *18*: 363-374, 1999; Zeng, H., Sanyal, S. and Mukhopadhyay, D., J. Biol. Chem., *276*: 32714-32719, 2001; Gille, H., Kowalski, J., Li, B., LeCouter, J., Moffat, B, Zioncheck, T.F., Pelletier, N. and Ferrara, N., J. Biol. Chem., *276*: 3222-3230, 2001).

International patent applications publication numbers WO 98/13354, WO 01/32651 and WO 01/77085 describe VEGF receptor tyrosine kinase inhibitors. International patent application publication number WO 01/21594 describes a broad scope of quinazoline derivatives but with a different activity to those of the present invention; compounds of WO 01/21594 inhibit aurora-2 kinase. Compounds of WO 98/13354 and WO 01/32651 possess activity against VEGF receptor tyrosine kinase (RTK) and also possess some activity against epidermal growth factor (EGF) RTK. International patent application publication number WO 02/18372 and European Patent Application No. EP0566226 describe anilinoquinazolines which inhibit EGF RTK. The compounds of WO 98/13354 and WO 01/32651 are generally more potent against KDR than against Flt-1 and generally they are more potent against VEGF RTK than against EGF RTK. A potential problem with some VEGF RTK inhibitors is that they have been found to act as potassium channel blockers and are positive in a hERG assay; such activity may give rise to ECG (electrocardiogram) changes *in vivo*.

Surprisingly we have now found compounds of the present invention to be potent KDR and/or Flt-1 inhibitors as well as potent inhibitors of EGF RTK and to be inactive or only weakly active in a hERG assay.

According to one aspect of the present invention there is provided a compound of the formula I:



(I)

wherein:

Z is -NH-, -O- or -S-;

R^1 represents bromo or chloro;

R^3 represents C_{1-3}alkoxy or hydrogen;

R^2 is selected from one of the following three groups:

(i) Q^1X^1-

wherein X^1 represents -O-,-S- or -NR^4- wherein R^4 is hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl and Q^1 is selected from one of the following ten groups:

1) Q^2 (wherein Q^2 is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which heterocyclic group may optionally bear a further 1 or 2 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl), or Q^2 bears a single substituent selected from methylenedioxy and ethylenedioxy);

with the proviso that if Q^1 is Q^2 and X^1 is -O- then Q^2 must bear at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, and di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl and optionally may bear a further 1 or 2 substituents as defined hereinbefore;

2) C_{1-5}alkylW^1Q^2 (wherein W^1 represents -O-, -S-, -SO-, -SO_2-, -C(O)-, -OC(O)-, -NQ^3C(O)-, -C(O)NQ^4-, -SO_2NQ^5-, -NQ^6SO_2- or –NQ^7- (wherein Q^3, Q^4, Q^5, Q^6 and Q^7 each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl) and Q^2 is as defined hereinbefore;

3) C_{1-5}alkylQ^2 (wherein Q^2 is as defined hereinbefore);

4) C_{2-5}alkenylQ^2 (wherein Q^2 is as defined hereinbefore);

5) C_{2-5}alkynylQ^2 (wherein Q^2 is as defined hereinbefore);

6) C_{1-4}alkylW^2C_{1-4}alkylQ^2 (wherein W^2 represents -O-, -S-, -SO-, -SO_2-, -C(O)-, -OC(O)- -NQ^8C(O)-, -C(O)NQ^9-, -SO_2NQ^{10}-, -$NQ^{11}SO_2$- or –NQ^{12}- (wherein Q^8, Q^9, Q^{10}, Q^{11} and Q^{12} each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl) and Q^2 is as defined hereinbefore);

7) C_{2-5}alkenylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

8) C_{2-5}alkynylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

9) C_{1-4}alkylQ^{13}(C_{1-4}alkyl)$_j$(W^2)$_k$$Q^{14}$ (wherein W^2 is as defined hereinbefore, j is 0 or 1, k is 0 or 1, and Q^{13} and Q^{14} are each independently selected from hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1, 2 or 3 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or more substituents selected from C_{1-4}alkyl), with the provisos that Q^{13} cannot be hydrogen and one or both of Q^{13} and Q^{14} must be a 5-6-membered saturated or partially unsaturated heterocyclic group as defined hereinbefore which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which

heterocyclic group optionally bears 1 or 2 further substituents selected from those defined hereinbefore); and

10) C_{1-4}alkylQ^{13}-C(O)-C_{1-4}alkylQ^{14n} wherein Q^{13} is as defined hereinbefore and is not hydrogen and Q^{14n} is a 5-6-membered saturated or partially unsaturated heterocyclic group containing at least one nitrogen atom and optionally containing a further heteroatom selected from N and O wherein Q^{14n} is linked to C_{1-6}alkyl via a nitrogen atom or a carbon atom and wherein Q^{14n} optionally bears 1, 2 or 3 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or more substituents selected from C_{1-4}alkyl) or Q^{14n} bears a single substituent selected from methylenedioxy and ethylenedioxy);

(ii) $Q^{15}W^3$-

wherein W^3 represents $-NQ^{16}C(O)-$, $-C(O)NQ^{17}-$, $-SO_2NQ^{18}-$, $-NQ^{19}SO_2-$ or $-NQ^{20}-$ (wherein Q^{16}, Q^{17}, Q^{18}, Q^{19} and Q^{20} each independently represents C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}haloalkyl), and Q^{15} is C_{1-6}haloalkyl, C_{2-5}alkenyl or C_{2-5}alkynyl; and

(iii) $Q^{21}W^4C_{1-5}$alkylX^1 wherein X^1 is as defined hereinbefore, W^4 represents $-NQ^{22}C(O)-$, $-C(O)NQ^{23}-$, $-SO_2NQ^{24}-$, $-NQ^{25}SO_2-$ or $-NQ^{26}-$ (wherein Q^{22}, Q^{23}, Q^{24}, Q^{25} and Q^{26} each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl), and Q^{21} represents C_{1-6}haloalkyl, C_{2-5}alkenyl or C_{2-5}alkynyl;

or a salt thereof or a prodrug thereof.

According to one aspect of the present invention Z is -NH-.

According to one aspect of the present invention R^3 is methoxy.

According to one aspect of the present invention X^1 is -O-;

According to one aspect of the present invention R^4 is selected from group (i) of the groups (i), (ii) and (iii) defined hereinbefore.

According to one aspect of the present invention R^4 is selected from group (ii) of the groups (i), (ii) and (iii) defined hereinbefore.

According to one aspect of the present invention R^4 is selected from group (iii) of the groups (i), (ii) and (iii) defined hereinbefore.

According to one aspect of the present invention R^4 is selected from:

Q^1X^1-

wherein X^1 is as defined hereinbefore and Q^1 is selected from one of the following ten groups:

1) Q^2 (wherein Q^2 is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which heterocyclic group may optionally bear a further 1 or 2 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl),

or Q^2 bears a single substituent selected from methylenedioxy and ethylenedioxy);

with the proviso that if Q^1 is Q^2 and X^1 is -O- then Q^2 must bear at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, and di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl and optionally may bear a further 1 or 2 substituents as defined hereinbefore;

2) $C_{1\text{-}5}$alkylW^1Q^2 (wherein W^1 represents -O-, -S-, -SO-, $-SO_2-$, -C(O)-, -OC(O)-, $-NQ^3C(O)-$, $-C(O)NQ^4-$, $-SO_2NQ^5-$, $-NQ^6SO_2-$ or $-NQ^7-$ (wherein Q^3, Q^4, Q^5, Q^6 and Q^7 each independently represents hydrogen, $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$alkoxy$C_{2\text{-}3}$alkyl, $C_{2\text{-}5}$alkenyl, $C_{2\text{-}5}$alkynyl or $C_{1\text{-}4}$haloalkyl) and Q^2 is as defined hereinbefore;

3) $C_{1\text{-}5}$alkylQ^2 (wherein Q^2 is as defined hereinbefore);

4) $C_{2\text{-}5}$alkenylQ^2 (wherein Q^2 is as defined hereinbefore);

5) $C_{2\text{-}5}$alkynylQ^2 (wherein Q^2 is as defined hereinbefore);

6) $C_{1\text{-}4}$alkyl$W^2C_{1\text{-}4}$alkylQ^2 (wherein W^2 represents -O-, -S-, -SO-, $-SO_2-$, -C(O)-, -OC(O)- - $NQ^8C(O)-$, $-C(O)NQ^9-$, $-SO_2NQ^{10}-$, $-NQ^{11}SO_2-$ or $-NQ^{12}-$ (wherein Q^8, Q^9, Q^{10}, Q^{11} and Q^{12} each independently represents hydrogen, $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$alkoxy$C_{2\text{-}3}$alkyl, $C_{2\text{-}5}$alkenyl, $C_{2\text{-}5}$alkynyl or $C_{1\text{-}4}$haloalkyl) and Q^2 is as defined hereinbefore);

7) $C_{2\text{-}5}$alkenyl$W^2C_{1\text{-}4}$alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

8) $C_{2\text{-}5}$alkynyl$W^2C_{1\text{-}4}$alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

9) $C_{1\text{-}4}$alkyl$Q^{13}(C_{1\text{-}4}alkyl)_j(W^2)_kQ^{14}$ (wherein W^2 is as defined hereinbefore, j is 0 or 1, k is 0 or 1, and Q^{13} and Q^{14} are each independently selected from hydrogen, $C_{1\text{-}3}$alkyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which $C_{1\text{-}3}$alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $C_{1\text{-}4}$alkoxy and which cyclic group may bear 1, 2 or 3 substituents selected from $C_{2\text{-}5}$alkenyl, $C_{2\text{-}5}$alkynyl, $C_{1\text{-}6}$fluoroalkyl, $C_{1\text{-}6}$alkanoyl, amino$C_{2\text{-}6}$alkanoyl, $C_{1\text{-}4}$alkylamino$C_{2\text{-}6}$alkanoyl, di($C_{1\text{-}4}$alkyl)amino$C_{2\text{-}6}$alkanoyl, $C_{1\text{-}4}$alkoxy$C_{1\text{-}4}$alkylamino$C_{2\text{-}6}$alkanoyl, $C_{1\text{-}6}$fluoroalkanoyl, carbamoyl, $C_{1\text{-}4}$alkylcarbamoyl, di($C_{1\text{-}4}$alkyl)carbamoyl, carbamoyl$C_{1\text{-}6}$alkyl, $C_{1\text{-}4}$alkylcarbamoyl$C_{1\text{-}6}$alkyl, di($C_{1\text{-}4}$alkyl)carbamoyl$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkylsulphonyl, $C_{1\text{-}6}$fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, $C_{1\text{-}4}$cyanoalkyl, $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$hydroxyalkyl, $C_{1\text{-}4}$alkoxy, $C_{1\text{-}4}$alkoxy$C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylsulphonyl$C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxycarbonyl, $C_{1\text{-}4}$aminoalkyl, $C_{1\text{-}4}$alkylamino, di($C_{1\text{-}4}$alkyl)amino, $C_{1\text{-}4}$alkylamino$C_{1\text{-}4}$alkyl, di($C_{1\text{-}4}$alkyl)amino$C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylamino$C_{1\text{-}4}$alkoxy, di($C_{1\text{-}4}$alkyl)amino$C_{1\text{-}4}$alkoxy and a group $-(-O-)_f(C_{1\text{-}4}alkyl)_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or more substituents selected from $C_{1\text{-}4}$alkyl), with the provisos that Q^{13} cannot be hydrogen and one or both of Q^{13} and Q^{14} must be a 5-6-membered saturated or partially unsaturated heterocyclic group as defined hereinbefore which heterocyclic group bears at least one substituent selected from $C_{2\text{-}5}$alkenyl, $C_{2\text{-}5}$alkynyl, $C_{1\text{-}6}$fluoroalkyl, $C_{1\text{-}}$

$_6$alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which heterocyclic group optionally bears 1 or 2 further substituents selected from those defined hereinbefore); and

10) C_{1-4}alkylQ^{13}-C(O)-C_{1-4}alkylQ^{14a} wherein Q^{13} is as defined hereinbefore and is not hydrogen and Q^{14a} is a 5-6-membered saturated or partially unsaturated heterocyclic group containing at least one nitrogen atom and optionally containing a further heteroatom selected from N and O wherein Q^{14a} is linked to C_{1-6}alkyl via a nitrogen atom and wherein Q^{14a} optionally bears 1, 2 or 3 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or more substituents selected from C_{1-4}alkyl) or Q^{14a} bears a single substituent selected from methylenedioxy and ethylenedioxy).

According to one aspect of the present invention R^4 is selected from:

Q^1X^1-

wherein X^1 is as defined hereinbefore and Q^1 is selected from one of the following ten groups:

1) Q^2 (wherein Q^2 is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which heterocyclic group may optionally bear a further 1 or 2 substituents selected from C_{2-5}alkenyl,

$C_{2\text{-}5}$alkynyl, $C_{1\text{-}6}$fluoroalkyl, $C_{1\text{-}6}$alkanoyl, amino$C_{2\text{-}6}$alkanoyl, $C_{1\text{-}4}$alkylamino$C_{2\text{-}6}$alkanoyl, di($C_{1\text{-}4}$alkyl)amino$C_{2\text{-}6}$alkanoyl, $C_{1\text{-}4}$alkoxy$C_{1\text{-}4}$alkylamino$C_{2\text{-}6}$alkanoyl, $C_{1\text{-}6}$fluoroalkanoyl, carbamoyl, $C_{1\text{-}4}$alkylcarbamoyl, di($C_{1\text{-}4}$alkyl)carbamoyl, carbamoyl$C_{1\text{-}6}$alkyl, $C_{1\text{-}4}$alkylcarbamoyl$C_{1\text{-}6}$alkyl, di($C_{1\text{-}4}$alkyl)carbamoyl$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkylsulphonyl, $C_{1\text{-}6}$fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, $C_{1\text{-}4}$cyanoalkyl, $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$hydroxyalkyl, $C_{1\text{-}4}$alkoxy, $C_{1\text{-}4}$alkoxy$C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylsulphonyl$C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxycarbonyl, $C_{1\text{-}4}$aminoalkyl, $C_{1\text{-}4}$alkylamino, di($C_{1\text{-}4}$alkyl)amino, $C_{1\text{-}4}$alkylamino$C_{1\text{-}4}$alkyl, di($C_{1\text{-}4}$alkyl)amino$C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkylamino$C_{1\text{-}4}$alkoxy, di($C_{1\text{-}4}$alkyl)amino$C_{1\text{-}4}$alkoxy and a group -(-O-)$_f$($C_{1\text{-}4}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1\text{-}4}$alkyl),

or Q^2 bears a single substituent selected from methylenedioxy and ethylenedioxy);

with the proviso that if Q^1 is Q^2 and X^1 is -O- then Q^2 must bear at least one substituent selected from $C_{2\text{-}5}$alkenyl, $C_{2\text{-}5}$alkynyl, $C_{1\text{-}4}$alkoxy$C_{1\text{-}4}$alkylamino$C_{2\text{-}6}$alkanoyl, carbamoyl$C_{1\text{-}6}$alkyl, $C_{1\text{-}4}$alkylcarbamoyl$C_{1\text{-}6}$alkyl, and di($C_{1\text{-}4}$alkyl)carbamoyl$C_{1\text{-}6}$alkyl and optionally may bear a further 1 or 2 substituents as defined hereinbefore;

2) $C_{1\text{-}5}$alkylW^1Q^2 (wherein W^1 represents -O-, -S-, -SO-, -SO_2-, -C(O)-, -OC(O)-, -NQ^3C(O)-, -C(O)NQ^4-, -SO_2NQ^5-, -NQ^6SO_2- or –NQ^7- (wherein Q^3, Q^4, Q^5, Q^6 and Q^7 each independently represents hydrogen, $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$alkoxy$C_{2\text{-}3}$alkyl, $C_{2\text{-}5}$alkenyl, $C_{2\text{-}5}$alkynyl or $C_{1\text{-}4}$haloalkyl) and Q^2 is as defined hereinbefore;

3) $C_{1\text{-}5}$alkylQ^2 (wherein Q^2 is as defined hereinbefore);

4) $C_{2\text{-}5}$alkenylQ^2 (wherein Q^2 is as defined hereinbefore);

5) $C_{2\text{-}5}$alkynylQ^2 (wherein Q^2 is as defined hereinbefore);

6) $C_{1\text{-}4}$alkyl$W^2C_{1\text{-}4}$alkylQ^2 (wherein W^2 represents -O-, -S-, -SO-, -SO_2-, -C(O)-, -OC(O)- -NQ^8C(O)-, -C(O)NQ^9-, -SO_2NQ^{10}-, -$NQ^{11}SO_2$- or –NQ^{12}- (wherein Q^8, Q^9, Q^{10}, Q^{11} and Q^{12} each independently represents hydrogen, $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$alkoxy$C_{2\text{-}3}$alkyl, $C_{2\text{-}5}$alkenyl, $C_{2\text{-}5}$alkynyl or $C_{1\text{-}4}$haloalkyl) and Q^2 is as defined hereinbefore);

7) $C_{2\text{-}5}$alkenyl$W^2C_{1\text{-}4}$alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

8) $C_{2\text{-}5}$alkynyl$W^2C_{1\text{-}4}$alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

9) $C_{1\text{-}4}$alkylQ^{13}($C_{1\text{-}4}$alkyl)$_j$(W^2)$_k$$Q^{14}$ (wherein W^2 is as defined hereinbefore, j is 0 or 1, k is 0 or 1, and Q^{13} and Q^{14} are each independently selected from hydrogen, $C_{1\text{-}3}$alkyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2

heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1, 2 or 3 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or more substituents selected from C_{1-4}alkyl), with the provisos that Q^{13} cannot be hydrogen and one or both of Q^{13} and Q^{14} must be a 5-6-membered saturated or partially unsaturated heterocyclic group as defined hereinbefore which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which heterocyclic group optionally bears 1 or 2 further substituents selected from those defined hereinbefore); and

10) C_{1-4}alkylQ^{13}-C(O)-C_{1-4}alkylQ^{14a} wherein Q^{13} is as defined hereinbefore and is not hydrogen and Q^{14a} is a 5-6-membered saturated or partially unsaturated heterocyclic group containing at least one nitrogen atom and optionally containing a further heteroatom selected from N and O wherein Q^{14a} is linked to C_{1-6}alkyl via a nitrogen atom and wherein Q^{14a} optionally bears 1, 2 or 3 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-}

$_{4}$alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_{f}$(C_{1-4}alkyl)$_{g}$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or more substituents selected from C_{1-4}alkyl)
or Q^{14a} bears a single substituent selected from methylenedioxy and ethylenedioxy).

According to one aspect of the present invention R^4 is selected from:

Q^1X^1-

wherein X^1 is as defined hereinbefore and Q^1 is selected from one of the following nine groups:

1) Q^2 (wherein Q^2 is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which heterocyclic group may optionally bear a further 1 or 2 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_{f}$(C_{1-4}alkyl)$_{g}$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl),
or Q^2 bears a single substituent selected from methylenedioxy and ethylenedioxy);
with the proviso that if Q^1 is Q^2 and X^1 is -O- then Q^2 must bear at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, carbamoylC_{1-}

${}_{6}$alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, and di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl and optionally may bear a further 1 or 2 substituents as defined hereinbefore;

2) C_{1-5}alkylW^1Q^2 (wherein W^1 represents -O-, -S-, -SO-, -SO_2-, -C(O)-, -OC(O)-, -NQ^3C(O)-, -C(O)NQ^4-, -SO_2NQ^5-, -NQ^6SO_2- or –NQ^7- (wherein Q^3, Q^4, Q^5, Q^6 and Q^7 each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl) and Q^2 is as defined hereinbefore;

3) C_{1-5}alkylQ^2 (wherein Q^2 is as defined hereinbefore);

4) C_{2-5}alkenylQ^2 (wherein Q^2 is as defined hereinbefore);

5) C_{2-5}alkynylQ^2 (wherein Q^2 is as defined hereinbefore);

6) C_{1-4}alkylW^2C_{1-4}alkylQ^2 (wherein W^2 represents -O-, -S-, -SO-, -SO_2-, -C(O)-, -OC(O)- -NQ^8C(O)-, -C(O)NQ^9-, -SO_2NQ^{10}-, -$NQ^{11}SO_2$- or –NQ^{12}- (wherein Q^8, Q^9, Q^{10}, Q^{11} and Q^{12} each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl) and Q^2 is as defined hereinbefore);

7) C_{2-5}alkenylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

8) C_{2-5}alkynylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore); and

9) C_{1-4}alkylQ^{13}(C_{1-4}alkyl)$_j$(W^2)$_k$$Q^{14}$ (wherein W^2 is as defined hereinbefore, j is 0 or 1, k is 0 or 1, and Q^{13} and Q^{14} are each independently selected from hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1, 2 or 3 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or more substituents selected from C_{1-4}alkyl), with the provisos that Q^{13} cannot be hydrogen and one or both of Q^{13} and Q^{14} must be a 5-6-membered saturated or

partially unsaturated heterocyclic group as defined hereinbefore which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which heterocyclic group optionally bears 1 or 2 further substituents selected from those defined hereinbefore).

According to one aspect of the present invention R^4 is selected from:

Q^1X^1-

wherein X^1 is as defined hereinbefore and Q^1 is selected from one of the following eight groups:

1) Q^2 (wherein Q^2 is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which heterocyclic group may optionally bear a further 1 or 2 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl),

or Q^2 bears a single substituent selected from methylenedioxy and ethylenedioxy);

with the proviso that if Q^1 is Q^2 and X^1 is -O- then Q^2 must bear at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, and di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl and optionally may bear a further 1 or 2 substituents as defined hereinbefore;

2) C_{1-5}alkylW^1Q^2 (wherein W^1 represents -O-, -S-, -SO-, -SO_2-, -C(O)-, -OC(O)-, -NQ^3C(O)-, -C(O)NQ^4-, -SO_2NQ^5-, -NQ^6SO_2- or –NQ^7- (wherein Q^3, Q^4, Q^5, Q^6 and Q^7 each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl) and Q^2 is as defined hereinbefore;

3) C_{1-5}alkylQ^2 (wherein Q^2 is as defined hereinbefore);

4) C_{2-5}alkenylQ^2 (wherein Q^2 is as defined hereinbefore);

5) C_{2-5}alkynylQ^2 (wherein Q^2 is as defined hereinbefore);

6) C_{1-4}alkylW^2C_{1-4}alkylQ^2 (wherein W^2 represents -O-, -S-, -SO-, -SO_2-, -C(O)-, -OC(O)- -NQ^8C(O)-, -C(O)NQ^9-, -SO_2NQ^{10}-, -$NQ^{11}SO_2$- or –NQ^{12}- (wherein Q^8, Q^9, Q^{10}, Q^{11} and Q^{12} each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl) and Q^2 is as defined hereinbefore);

7) C_{2-5}alkenylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore); and

8) C_{2-5}alkynylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore).

According to one aspect of the present invention there is provided a compound of the formula I as defined hereinbefore

wherein Z, R^1 and R^3 are as defined hereinbefore and

R^2 is Q^1X^1-

wherein X^1 represents -O-,-S- or -NR^4- wherein R^4 is hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl and Q^1 is selected from one of the following ten groups:

1) Q^2 (wherein Q^2 is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group bears at least one substituent selected from aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl and di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl and which heterocyclic group may optionally bear a further 1 or 2 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-}

$_6$fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C_{1-4}alkyl),

or Q^2 bears a single substituent selected from methylenedioxy and ethylenedioxy);

with the proviso that if Q^1 is Q^2 and X^1 is -O- then Q^2 must bear at least one substituent selected from C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, and di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl and optionally may bear a further 1 or 2 substituents as defined hereinbefore;

2) C_{1-5}alkylW^1Q^2 (wherein W^1 represents -O-, -S-, -SO-, -SO_2-, -C(O)-, -OC(O)-, -NQ^3C(O)-, -C(O)NQ^4-, -SO_2NQ^5-, -NQ^6SO_2- or -NQ^7- (wherein Q^3, Q^4, Q^5, Q^6 and Q^7 each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl) and Q^2 is as defined hereinbefore;

3) C_{1-5}alkylQ^2 (wherein Q^2 is as defined hereinbefore);

4) C_{2-5}alkenylQ^2 (wherein Q^2 is as defined hereinbefore);

5) C_{2-5}alkynylQ^2 (wherein Q^2 is as defined hereinbefore);

6) C_{1-4}alkylW^2C_{1-4}alkylQ^2 (wherein W^2 represents -O-, -S-, -SO-, -SO_2-, -C(O)-, -OC(O)- -NQ^8C(O)-, -C(O)NQ^9-, -SO_2NQ^{10}-, -$NQ^{11}SO_2$- or -NQ^{12}- (wherein Q^8, Q^9, Q^{10}, Q^{11} and Q^{12} each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl) and Q^2 is as defined hereinbefore);

7) C_{2-5}alkenylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

8) C_{2-5}alkynylW^2C_{1-4}alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

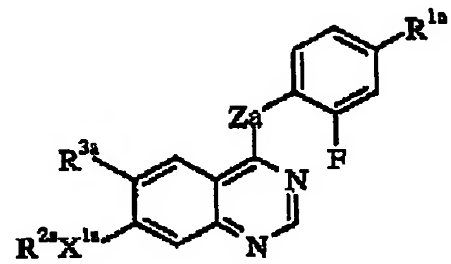
9) C_{1-4}alkylQ^{13}(C_{1-4}alkyl)$_j$(W^2)$_k$$Q^{14}$ (wherein W^2 is as defined hereinbefore, j is 0 or 1, k is 0 or 1, and Q^{13} and Q^{14} are each independently a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1, 2 or 3 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-}

$_4$alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or more substituents selected from C_{1-4}alkyl), with the proviso that one or both of Q^{13} and Q^{14} bears at least one substituent selected from aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl and di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, and which heterocyclic group optionally bears 1 or 2 further substituents selected from those defined hereinbefore); and

10) C_{1-4}alkylQ^{13}-C(O)-C_{1-4}alkylQ^{14n} wherein Q^{13} is as defined hereinbefore and Q^{14n} is a 5-6-membered saturated or partially unsaturated heterocyclic group containing at least one nitrogen atom and optionally containing a further heteroatom selected from N and O wherein Q^{14n} is linked to C_{1-6}alkyl via a nitrogen atom or a carbon atom and wherein Q^{14n} optionally bears 1, 2 or 3 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or more substituents selected from C_{1-4}alkyl) or Q^{14n} bears a single substituent selected from methylenedioxy and ethylenedioxy);

or a salt thereof or a prodrug thereof.

According to another aspect of the present invention there is provided a compound according to formula I of the formula Ia:



(Ia)

wherein:

Za is -NH-, -O- or -S-;

R^{1a} represents bromo or chloro;

R^{3a} represents C_{1-3}alkoxy or hydrogen;

X^{1a} represents -O-,-S- or -NR^{4a}- wherein R^{4a} is hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl;

R^{2a} is selected from one of the following groups:

1) C_{1-5}alkylR^{5a} (wherein R^{5a} is a 5- or 6-membered heterocyclic ring selected from morpholine, pyrrolidine, piperidine and piperazine which heterocyclic ring bears at least one substituent selected from aminoC_{2-4}alkanoyl, C_{1-4}alkylaminoC_{2-4}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-4}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-4}alkanoyl, methylenedioxy and ethylenedioxy);

2) C_{2-5}alkenylR^{5a} (wherein R^{5a} is as defined hereinbefore);

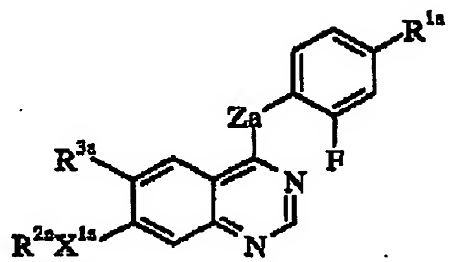
3) C_{2-5}alkynylR^{5a} (wherein R^{5a} is as defined hereinbefore);

4) C_{1-5}alkylR^{6a}C(O)$(CH_2)_{ma}R^{7a}$ (wherein ma is 1 or 2, R^{6a} is a 5- or 6-membered heterocyclic ring selected from morpholine, pyrrolidine, piperidine and piperazine which heterocyclic ring may bear one or two substituents selected from fluoro, hydroxy and methyl, and R^{7a} is a 5- or 6-membered heterocyclic ring selected from pyrrolidine, piperidine, piperazine and morpholine which heterocyclic ring is linked to $(CH_2)_{ma}$ via a nitrogen atom or a carbon atom and which heterocyclic ring may bear one or more substituents selected from hydroxy, halogeno, C_{1-4}alkanoyl, methylenedioxy and ethylenedioxy); and

5) C_{1-5}alkyl$R^{6a}(CH_2)_{ma}$C(O)R^{8a} (wherein ma and R^{6a} are as defined hereinbefore and R^{8a} is a 5- or 6-membered heterocyclic ring selected from pyrrolidine, piperidine, piperazine and morpholine which heterocyclic ring is linked to C(O) via a nitrogen atom or a carbon atom and which heterocyclic ring may bear one or more substituents selected from hydroxy, halogeno, C_{1-4}alkanoyl, methylenedioxy and ethylenedioxy)

or a salt thereof.

According to another aspect of the present invention there is provided a compound according to formula I of the formula Ia:



(Ia)

wherein:

Za, R^{1a}, R^{3a} and X^{1a} are as described hereinbefore and

R^{2a} is selected from one of the following groups:

1) C_{1-5}alkylR^{5a} (wherein R^{5a} is a 5- or 6-membered heterocyclic ring selected from morpholine, pyrrolidine, piperidine and piperazine which heterocyclic ring bears at least one substituent selected from aminoC_{2-4}alkanoyl, C_{1-4}alkylaminoC_{2-4}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-4}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-4}alkanoyl, methylenedioxy and ethylenedioxy);

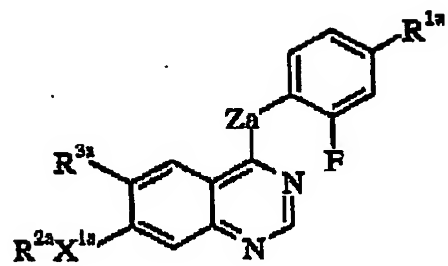
2) C_{2-5}alkenylR^{5a} (wherein R^{5a} is as defined hereinbefore);

3) C_{2-5}alkynylR^{5a} (wherein R^{5a} is as defined hereinbefore); and

4) C_{1-5}alkylR^{6a}C(O)$(CH_2)_{ma}R^{7a}$ (wherein ma is 1 or 2, R^{6a} is a 5- or 6-membered heterocyclic ring selected from morpholine, pyrrolidine, piperidine and piperazine which heterocyclic ring may bear one or two substituents selected from fluoro, hydroxy and methyl, and R^{7a} is a 5- or 6-membered heterocyclic ring selected from pyrrolidine, piperidine, piperazine and morpholine which heterocyclic ring is linked to $(CH_2)_{ma}$ via a nitrogen atom or a carbon atom and which heterocyclic ring may bear one or more substituents selected from hydroxy, halogeno, C_{1-4}alkanoyl, methylenedioxy and ethylenedioxy);

or a salt thereof.

According to another aspect of the present invention there is provided a compound according to formula I of the formula Ia:



(Ia)

wherein:

Za, R^{1a}, R^{3a} and X^{1a} are as described hereinbefore and

R^{2a} is selected from one of the following groups:

1) $C_{1\text{-}5}$alkylR^{5a} (wherein R^{5a} is a 5- or 6-membered heterocyclic ring selected from morpholine, pyrrolidine, piperidine and piperazine which heterocyclic ring bears at least one substituent selected from amino$C_{2\text{-}4}$alkanoyl, $C_{1\text{-}4}$alkylamino$C_{2\text{-}4}$alkanoyl, di($C_{1\text{-}4}$alkyl)amino$C_{2\text{-}4}$alkanoyl, $C_{1\text{-}4}$alkoxy$C_{1\text{-}4}$alkylamino$C_{2\text{-}4}$alkanoyl, methylenedioxy and ethylenedioxy);

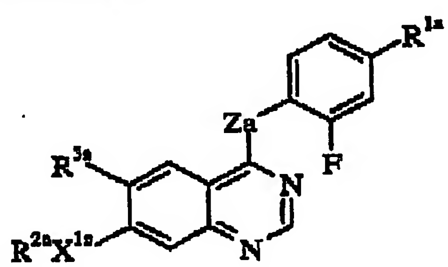
2) $C_{2\text{-}5}$alkenylR^{5a} (wherein R^{5a} is as defined hereinbefore);

3) $C_{2\text{-}5}$alkynylR^{5a} (wherein R^{5a} is as defined hereinbefore); and

4) $C_{1\text{-}5}$alkyl$R^{6a}C(O)(CH_2)_{ma}R^{7a}$ (wherein ma is 1 or 2, R^{6a} is a 5- or 6-membered heterocyclic ring selected from morpholine, pyrrolidine, piperidine and piperazine which heterocyclic ring may bear one or two substituents selected from fluoro, hydroxy and methyl, and R^{7a} is a 5- or 6-membered heterocyclic ring selected from pyrrolidine, piperidine, piperazine and morpholine which heterocyclic ring is linked to $(CH_2)_{ma}$ via a nitrogen atom and which heterocyclic ring may bear one or more substituents selected from hydroxy, halogeno, $C_{1\text{-}4}$alkanoyl, methylenedioxy and ethylenedioxy);

or a salt thereof.

According to another aspect of the present invention there is provided a compound according to formula I of the formula Ia:



(Ia)

wherein:

Za, R^{1a}, R^{3a} and X^{1a} are as described hereinbefore and

R^{2a} is selected from one of the following groups:

1) C_{1-5}alkylR^{5a} (wherein R^{5a} is a 5- or 6-membered heterocyclic ring selected from morpholine, pyrrolidine, piperidine and piperazine which heterocyclic ring bears at least one substituent selected from aminoC_{2-4}alkanoyl, C_{1-4}alkylaminoC_{2-4}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-4}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-4}alkanoyl, methylenedioxy and ethylenedioxy);

2) C_{2-5}alkenylR^{5a} (wherein R^{5a} is as defined hereinbefore); and

3) C_{2-5}alkynylR^{5a} (wherein R^{5a} is as defined hereinbefore);

or a salt thereof.

According to one aspect of the present invention R^{2a} is C_{1-5}alkylR^{5a} (wherein R^{5a} is a 5- or 6-membered heterocyclic ring selected from morpholine, pyrrolidine, piperidine and piperazine which heterocyclic ring bears at least one substituent selected from aminoC_{2-4}alkanoyl, C_{1-4}alkylaminoC_{2-4}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-4}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-4}alkanoyl, methylenedioxy and ethylenedioxy).

According to one aspect of the present invention R^{2a} is C_{1-5}alkyl$R^{6a}C(O)(CH_2)_{ma}R^{7a}$ (wherein ma is 1 or 2, R^{6a} is a 5- or 6-membered heterocyclic ring selected from morpholine, pyrrolidine, piperidine and piperazine which heterocyclic ring may bear one or two substituents selected from fluoro, hydroxy and methyl, and R^{7a} is a 5- or 6-membered heterocyclic ring selected from pyrrolidine, piperidine, piperazine and morpholine which heterocyclic ring is linked to $(CH_2)_{ma}$ via a nitrogen atom or a carbon atom and which heterocyclic ring may bear one or more substituents selected from hydroxy, halogeno, C_{1-4}alkanoyl, methylenedioxy and ethylenedioxy).

According to one aspect of the present invention Za is -NH-.

According to one aspect of the present invention R^{3a} is methoxy.

According to one aspect of the present invention X^{1a} is -O-;

Particular compounds of the present invention include:

4-(4-bromo-2-fluoroanilino)-7-({1-[(*N,N*- dimethylamino)acetyl]piperidin-4-yl}methoxy)-6-methoxyquinazoline,

4-(4-chloro-2-fluoroanilino)-7-({1-[(*N,N*-dimethylamino)acetyl]piperidin-4-yl}methoxy)-6-methoxyquinazoline,

4-(4-chloro-2-fluoroanilino)-6-methoxy-7-{[1-(pyrrolidin-1-ylacetyl)piperidin-4-yl]methoxy}quinazoline,
4-(4-chloro-2-fluoroanilino)-6-methoxy-7-{[1-(piperidin-1-ylacetyl)piperidin-4-yl]methoxy}quinazoline,
4-(4-chloro-2-fluoroanilino)-6-methoxy-7-{[1-(morpholin-4-ylacetyl)piperidin-4-yl]methoxy}quinazoline,
4-(4-chloro-2-fluoroanilino)-6-methoxy-7-({1-[(3a*R*,6a*S*)-tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-ylacetyl]piperidin-4-yl}methoxy)quinazoline,
7-({1-[(4-acetylpiperazin-1-yl)acetyl]piperidin-4-yl}methoxy)-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline,
(3*S*)-7-({1-[(3-hydroxypyrrolidin-1-yl)acetyl]piperidin-4-yl}methoxy)-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline,
4-(4-chloro-2-fluoroanilino)-6-methoxy-7-[(1-{[*N*-(2-methoxyethyl)amino]acetyl}piperidin-4-yl)methoxy]quinazoline,
4-(4-chloro-2-fluoroanilino)-6-methoxy-7-({1-[(*N*-methylamino)acetyl]piperidin-4-yl}methoxy)quinazoline,
4-(4-chloro-2-fluoroanilino)-7-({1-[(3,3-difluoropyrrolidin-1-yl)acetyl]piperidin-4-yl}methoxy)-6-methoxyquinazoline,
4-(4-chloro-2-fluoroanilino)-7-(2-{1-[(*N*,*N*-dimethylamino)acetyl]piperidin-4-yl}ethoxy)-6-methoxyquinazoline,
4-(4-bromo-2-fluoroanilino)-7-(2-{1-[(*N*,*N*-dimethylamino)acetyl]piperidin-4-yl}ethoxy)-6-methoxyquinazoline,
4-(4-chloro-2-fluoroanilino)-7-({(3*R*)-1-[(*N*,*N*-dimethylamino)acetyl]piperidin-3-yl}methoxy)-6-methoxyquinazoline,
4-(4-Chloro-2-fluoroanilino)-7-({(3*S*)-1-[(*N*,*N*-dimethylamino)acetyl]piperidin-3-yl}methoxy)-6-methoxyquinazoline,
4-(4-bromo-2-fluoroanilino-6-methoxy-7-{3-[(3a*R*,6a*S*)-tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-yl]propoxy}quinazoline,
4-(4-bromo-2-fluoroanilino)-6-methoxy-7-{2-[(3a*R*,6a*S*)-tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-yl]ethoxy}quinazoline,
and salts thereof.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore' the said group

encompasses the first occurring and broadest definition as well as each and all of the preferred definitions for that group.

In this specification unless stated otherwise the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms. Unless otherwise stated the term "alkyl" advantageously refers to chains with 1-6 carbon atoms, preferably 1-4 carbon atoms. The term "alkoxy" as used herein, unless stated otherwise includes "alkyl"-O- groups in which "alkyl" is as hereinbefore defined. The term "aryl" as used herein unless stated otherwise includes reference to a C_{6-10} aryl group which may, if desired, carry one or more substituents selected from halogeno, alkyl, alkoxy, nitro, trifluoromethyl and cyano, (wherein alkyl and alkoxy are as hereinbefore defined). The term "aryloxy" as used herein unless otherwise stated includes "aryl"-O-groups in which "aryl" is as hereinbefore defined. The term "sulphonyloxy" as used herein refers to alkylsulphonyloxy and arylsulphonyloxy groups in which "alkyl" and "aryl" are as hereinbefore defined. The term "alkanoyl" as used herein unless otherwise stated includes formyl and alkylC=O groups in which "alkyl" is as defined hereinbefore, for example C_2alkanoyl is ethanoyl and refers to $CH_3C{=}O$, C_1alkanoyl is formyl and refers to CHO. Butanoyl refers to CH_3-CH_2-CH_2-C(O), isobutyryl refers to $(CH_3)_2$.CH-C(O). In this specification unless stated otherwise the term "alkenyl" includes both straight and branched chain alkenyl groups but references to individual alkenyl groups such as 2-butenyl are specific for the straight chain version only. Unless otherwise stated the term "alkenyl" advantageously refers to chains with 2-5 carbon atoms, preferably 3-4 carbon atoms. In this specification unless stated otherwise the term "alkynyl" includes both straight and branched chain alkynyl groups but references to individual alkynyl groups such as 2-butynyl are specific for the straight chain version only. Unless otherwise stated the term "alkynyl" advantageously refers to chains with 2-5 carbon atoms, preferably 3-4 carbon atoms. Unless stated otherwise the term "haloalkyl" refers to an alkyl group as defined hereinbefore which bears one or more halogeno groups, such as for example trifluoromethyl.

Within the present invention it is to be understood that a compound of the formula I or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits VEGF receptor tyrosine kinase activity and is not to be limited merely to any one tautomeric form

utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It will be appreciated that compounds of the formula I or a salt thereof may possess an asymmetric carbon atom. Such an asymmetric carbon atom is also involved in the tautomerism described above, and it is to be understood that the present invention encompasses any chiral form (including both pure enantiomers, scalemic and racemic mixtures) as well as any tautomeric form which inhibits VEGF receptor tyrosine kinase activity, and is not to be limited merely to any one tautomeric form or chiral form utilised within the formulae drawings. It is to be understood that the invention encompasses all optical and diastereomers which inhibit VEGF receptor tyrosine kinase activity. It is further to be understood that in the names of chiral compounds (*R*,*S*) denotes any scalemic or racemic mixture while (*R*) and (*S*) denote the enantiomers. In the absence of (*R*,*S*), (*R*) or (*S*) in the name it is to be understood that the name refers to any scalemic or racemic mixture, wherein a scalemic mixture contains *R* and *S* enantiomers in any relative proportions and a racemic mixture contains *R* and *S* enantiomers in the ration 50:50.

It is also to be understood that certain compounds of the formula I and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit VEGF receptor tyrosine kinase activity.

For the avoidance of any doubt, it is to be understood that when X^1 is $-NR^4-$ it is the nitrogen atom bearing the R^4 group which is linked to the quinazoline ring and to Q^1 and an analogous convention applies to similar groups. When W^1 is, for example, a group of formula $-NQ^3C(O)-$, it is the nitrogen atom bearing the Q^3 group which is attached to the C_{1-5}alkyl group and the carbonyl (C(O)) group is attached to Q^2, whereas when W^1 is, for example, a group of formula $-C(O)NQ^4-$, it is the carbonyl group which is attached to the C_{1-5}alkyl group and the nitrogen atom bearing the Q^4 group is attached to Q^2. A similar convention applies to the other two atom W^1 linking groups such as $-NQ^6SO_2-$ and $-SO_2NQ^5-$. An analogous convention applies to other groups. It is further to be understood that when X^1 represents $-NR^4-$ and R^4 is C_{1-3}alkoxyC_{2-3}alkyl it is the C_{2-3}alkyl moiety which is linked to the nitrogen atom of X^1 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that in a compound of the formula I when Q^1 is, for example, a group of formula C_{1-4}alkylW^2C_{1-4}alkylQ^2, it is the terminal C_{1-4}alkyl moiety which is linked to X^1, which is in turn linked to the quinazoline ring, similarly when Q^1 is, for example, a group of formula C_{2-5}alkenylQ^2 it is the C_{2-5}alkenyl moiety which is linked to X^1 and an analogous convention applies to other groups. When Q^1 is a group 1-Q^2prop-1-en-3-yl it is the first carbon to which the group Q^2 is attached and it is the third carbon which is linked to X^1 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that in a compound of the formula I when Q^1 is, for example, Q^2 and Q^2 is a pyrrolidinyl ring which bears a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD, it is the -O- or C_{1-4}alkyl which is linked to the pyrrolidinyl ring, unless f and g are both 0 when it is ring D which is linked to the pyrrolidinyl ring and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when Q^2 carries a C_{1-4}aminoalkyl substituent it is the C_{1-4}alkyl moiety which is attached to Q^2 whereas when Q^2 carries a C_{1-4}alkylamino substituent it is the amino moiety which is attached to Q^2 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when Q^2 carries a C_{1-4}alkoxyC_{1-4}alkyl substituent it is the C_{1-4}alkyl moiety which is attached to Q^2 and an analogous convention applies to other groups.

For the avoidance of any doubt, it is to be understood that when R^2 is a group $Q^{15}W^3$ it is the W^3 group which is linked to the quinazoline ring.

For the avoidance of any doubt, it is to be understood that when R^2 is a group $Q^{21}W^4C_{1-5}$alkylX^1 it is the X^1 group which is linked to the quinazoline ring.

For the avoidance of any doubt, it is to be understood that when the phrase "a 5-6-membered saturated or partially unsaturated heterocyclic group" is used herein for the values of, for example, Q^2, ring D, Q^{13}, Q^{14} and Q^{14a} it does not include the value pyridone. Thus Q^2, ring D, Q^{13}, Q^{14} and Q^{14a} cannot be pyridone.

Compounds of formula I may be administered in the form of a prodrug which is broken down in the human or animal body to give a compound of the formula I. Examples of prodrugs include *in vivo* hydrolysable esters of a compound of the formula I.

Various forms of prodrugs are known in the art. For examples of such prodrug derivatives see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).

An *in vivo* hydrolysable ester of a compound of formula I containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and a-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of a-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

The present invention relates to the compounds of formula I as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula I as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. In addition where the compounds of formula I are sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium

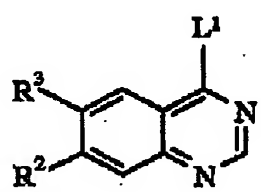
salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

A compound of the formula I, or salt thereof, and other compounds of the invention (as herein defined) may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes include, for example, those illustrated in International Patent Applications Publication Numbers WO 98/13354 and WO 01/32651, WO 97/22596, WO 97/30035, WO 97/32856 and in European Patent Applications Publication Nos. 0520722, 0566226, 0602851 and 0635498. Such processes also include, for example, solid phase synthesis. Such processes, are provided as a further feature of the invention and are as described hereinafter. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Thus the following processes (a) to (e) and (i) to (iv) constitute further features of the present invention.

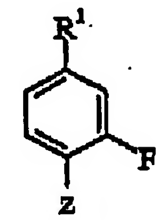
Synthesis of Compounds of Formula I

(a) Compounds of the formula I and salts thereof may be prepared by the reaction of a compound of the formula II:



(II)

(wherein R^2 and R^3 are as defined hereinbefore and L^1 is a displaceable moiety), with a compound of the formula III:



(III)

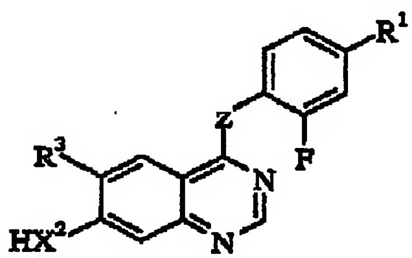
(wherein R^1 and Z are as defined hereinbefore) whereby to obtain compounds of the formula I and salts thereof. A convenient displaceable moiety L^1 is, for example, a halogeno, alkoxy (preferably C_{1-4}alkoxy), aryloxy or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group.

The reaction is advantageously effected in the presence of either an acid or a base. Such an acid is, for example, an anhydrous inorganic acid such as hydrogen chloride. Such a base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or for example, an alkali metal or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively such a base is, for example, an alkali metal hydride, for example sodium hydride, or an alkali metal or alkaline earth metal amide, for example sodium amide or sodium bis(trimethylsilyl)amide. The reaction is preferably effected in the presence of an inert solvent or diluent, for example an alkanol or ester such as methanol, ethanol, 2-propanol or ethyl acetate, a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently effected at a temperature in the range, for example, 10 to 150°C, preferably in the range 20 to 80°C.

The compound of the invention may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of the formula H-L^1 wherein L^1 has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a base as defined hereinbefore using a conventional procedure.

When it is desired to obtain the acid salt, the free base may be treated with an acid such as a hydrogen halide, for example hydrogen chloride, sulphuric acid, a sulphonic acid, for example methane sulphonic acid, or a carboxylic acid, for example acetic or citric acid, using a conventional procedure.

(b) Compounds of the formula I and salts thereof may be prepared by the reaction, conveniently in the presence of a base as defined hereinbefore, of a compound of the formula IV:



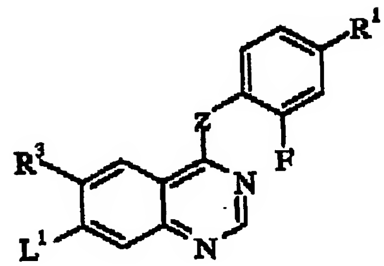
(IV)

(wherein Z, R^1 and R^3 are as hereinbefore defined) with a compound of formula V:

$$R^5\text{-}L^1 \qquad (V)$$

(wherein R^5 is Q^1, Q^{15} or $Q^{21}W^4C_{1\text{-}5}$alkyl, X^2 is X^1 or W^3 and L^1 is as hereinbefore defined); L^1 is a displaceable moiety for example a halogeno or sulphonyloxy group such as a bromo or methanesulphonyloxy group. Conveniently L^1 is a group $O\text{-}^{+}P(Y)_3$ (wherein Y is butyl or phenyl) and in such cases the compound of formula V is conveniently formed *in situ*. The reaction is preferably effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 50°C.

(c) Compounds of the formula I and salts thereof may be prepared by the reaction of a compound of the formula VI:



(VI)

with a compound of the formula VIIa-c:

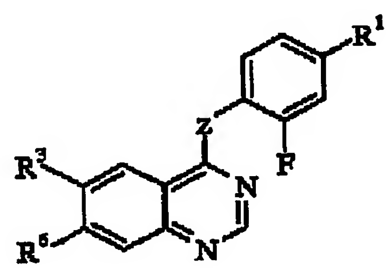
Q^1-X^1-H (VIIa)

Q^{15}-W^3-H (VIIb)

Q^{21}-W^4-C_{1-5}alkyl-X^1-H (VIIc)

(wherein L^1, R^1, R^3, Z, Q^1, Q^{15}, Q^{21} W^3, W^4 and X^1 are all as hereinbefore defined). The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 100°C.

(d) Compounds of the formula I and salts thereof may be prepared by the deprotection of a compound of the formula VIII:

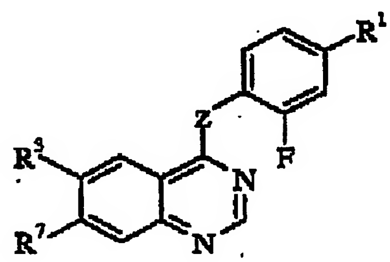


(VIII)

wherein R^1, R^3 and Z are all as hereinbefore defined, and R^6 represents a protected R^2 group wherein R^2 is as defined hereinbefore but additionally bears one or more protecting groups P^2. The choice of protecting group P^2 is within the standard knowledge of an organic chemist, for example those included in standard texts such as "Protective Groups in Organic Synthesis"

T.W. Greene and R.G.M.Wuts, 2nd Ed. Wiley 1991. Preferably P^2 is a protecting group such as a carbamate (alkoxycarbonyl) (such as, for example, *tert*-butoxycarbonyl, *tert*-amyloxycarbonyl, cyclobutoxycarbonyl, propoxycarbonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, allyloxycarbonyl or benzyloxycarbonyl). More preferably P^2 is *tert*-buto[illegible] Such an acid is, for example, an inorganic acid such as hydrogen chloride, hydrogen bromide or an organic acid such as trifluoro[illegible]ic acid, trifluoromethane sulphonic acid. The reaction may be effected in the presence of an inert solvent such as methylene chloride, trichloromethane and in the presence of a trace of water. The reaction is conveniently effected at a temperature in the range, for example, 10-100°C, preferably in the range 20-80°C.

(e) Compounds of the formula I and salts thereof may be prepared by the addition of a substituent to a compound of the formula IX:



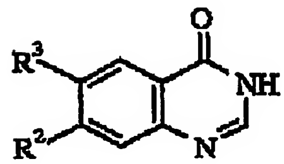
(IX)

wherein R^1, R^3 and Z are all as hereinbefore defined, and R^7 represents an R^2 group which has yet to be substituted with its final substituent.

For example where R^2 contains a heterocyclic ring with a substituent it is possible to add the substituent after process (a) above using standard procedures of organic chemistry. Thus for example a compound of formula II as defined hereinbefore but wherein R^2 contains an unsubstituted heterocyclic ring may be reacted with a compound of formula III as defined hereinbefore to give an intermediate compound in which R^2 contains an unsubstituted heterocyclic ring. The intermediate compound can then be substituted on the heterocyclic ring in R^2 using standard organic chemistry techniques to give a final compound of formula I.

<u>Synthesis of Intermediates</u>

(i) The compounds of formula III and salts thereof in which L^1 is halogeno may for example be prepared by halogenating a compound of the formula X:

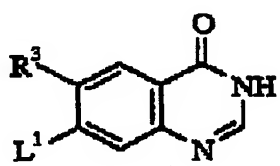


(X)

(wherein R^2 and R^3 are as hereinbefore defined).

Convenient halogenating agents include inorganic acid halides, for example thionyl chloride, phosphorus(III)chloride, phosphorus(V)oxychloride and phosphorus(V)chloride. The halogenation reaction is conveniently effected in the presence of an inert solvent or diluent such as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, or an aromatic hydrocarbon solvent such as benzene or toluene. The reaction is conveniently effected at a temperature in the range, for example 10 to 150°C, preferably in the range 40 to 100°C.

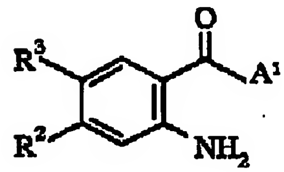
The compounds of formula X and salts thereof may for example be prepared by reacting a compound of the formula XI:



(XI)

(wherein R^3 and L^1 are as hereinbefore defined) with a compound of the formula VII as hereinbefore defined. The reaction may conveniently be effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently at about 100°C.

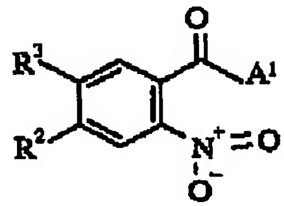
The compounds of formula X and salts thereof may also be prepared by cyclising a compound of the formula XII:



(XII)

(wherein R^2 and R^3, are as hereinbefore defined, and A^1 is an hydroxy, alkoxy (preferably C_{1-4}alkoxy) or amino group) whereby to form a compound of formula X or salt thereof. The cyclisation may be effected by reacting a compound of the formula XII, where A^1 is an hydroxy or alkoxy group, with formamide or an equivalent thereof effective to cause cyclisation whereby a compound of formula X or salt thereof is obtained, such as [3-(dimethylamino)-2-azaprop-2-enylidene]dimethylammonium chloride. The cyclisation is conveniently effected in the presence of formamide as solvent or in the presence of an inert solvent or diluent such as an ether for example 1,4-dioxan. The cyclisation is conveniently effected at an elevated temperature, preferably in the range 80 to 200°C. The compounds of formula X may also be prepared by cyclising a compound of the formula XII, where A^1 is an amino group, with formic acid or an equivalent thereof effective to cause cyclisation whereby a compound of formula X or salt thereof is obtained. Equivalents of formic acid effective to cause cyclisation include for example a tri-C_{1-4}alkoxymethane, for example triethoxymethane and trimethoxymethane. The cyclisation is conveniently effected in the presence of a catalytic amount of an anhydrous acid, such as a sulphonic acid for example p-toluenesulphonic acid, and in the presence of an inert solvent or diluent such as for example a halogenated solvent such as methylene chloride, trichloromethane or carbon tetrachloride, an ether such as diethyl ether or tetrahydrofuran, or an aromatic hydrocarbon solvent such as toluene. The cyclisation is conveniently effected at a temperature in the range, for example 10 to 100°C, preferably in the range 20 to 50°C.

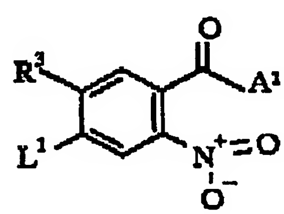
Compounds of formula XII and salts thereof may for example be prepared by the reduction of the nitro group in a compound of the formula XIII:



(XIII)

(wherein R^2, R^3 and A^1 are as hereinbefore defined) to yield a compound of formula XII as hereinbefore defined. The reduction of the nitro group may conveniently be effected by any of the procedures known for such a transformation. The reduction may be carried out, for example, by the hydrogenation of a solution of the nitro compound in the presence of an inert solvent or diluent as defined hereinbefore in the presence of a metal effective to catalyse hydrogenation reactions such as palladium or platinum. A further reducing agent is, for example, an activated metal such as activated iron (produced for example by washing iron powder with a dilute solution of an acid such as hydrochloric acid). Thus, for example, the reduction may be effected by heating the nitro compound and the activated metal in the presence of a solvent or diluent such as a mixture of water and alcohol, for example methanol or ethanol, to a temperature in the range, for example 50 to 150°C, conveniently at about 70°C.

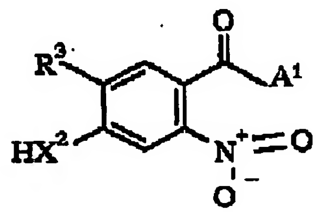
Compounds of the formula XIII and salts thereof may for example be prepared by the reaction of a compound of the formula XIV:



(XIV)

(wherein R^3, L^1 and A^1 are as hereinbefore defined) with a compound of the formula VII as hereinbefore defined to give a compound of the formual XIII. The reaction of the compounds of formulae XIV and VII is conveniently effected under conditions as described for process (c) hereinbefore.

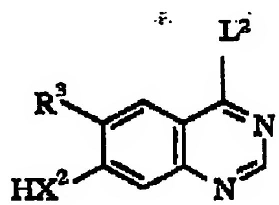
Compounds of formula XIII and salts thereof, may for example also be prepared by the reaction of a compound of the formula XV:



(XV)

(wherein R^3, X^2 and A^1 are as hereinbefore defined) with a compound of the formula V as hereinbefore defined to yield a compound of formula XIII as hereinbefore defined. The reaction of the compounds of formulae XV and V is conveniently effected under conditions as described for process (b) hereinbefore.

The compounds of formula II and salts thereof may also be prepared for example by reacting a compound of the formula XVI:

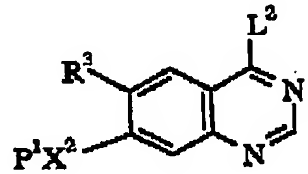


(XVI)

(wherein R^3 and X^2 are as hereinbefore defined and L^2 represents a displaceable protecting moiety) with a compound of the formula V as hereinbefore defined, whereby to obtain a compound of formula II in which L^1 is represented by L^2.

A compound of formula XVI is conveniently used in which L^2 represents a phenoxy group which may if desired carry up to 5 substituents, preferably up to 2 substituents, selected from halogeno, nitro and cyano. The reaction may be conveniently effected under conditions as described for process (b) hereinbefore.

The compounds of formula XVI and salts thereof as hereinbefore defined may for example be prepared by deprotecting a compound of the formula XVII:



(XVII)

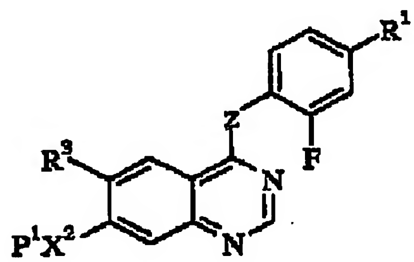
(wherein R^3, X^2 and L^2 are as hereinbefore defined and P^1 represents a phenolic hydroxy protecting group). The choice of phenolic hydroxy protecting group P^1 is within the standard knowledge of an organic chemist, for example those included in standard texts such as "Protective Groups in Organic Synthesis" T.W. Greene and R.G.M.Wuts, 2nd Ed. Wiley 1991, including ethers (for example, methyl, methoxymethyl, allyl and benzyl and benzyl substituted with up to two substituents selected from C_{1-4}alkoxy and nitro), silyl ethers (for example, t-butyldiphenylsilyl and t-butyldimethylsilyl), esters (for example, acetate and benzoate) and carbonates (for example, methyl and benzyl and benzyl substituted with up to two substituents selected from C_{1-4}alkoxy and nitro). Deprotection may be effected by techniques well known in the literature, for example where P^1 represents a benzyl group deprotection may be effected by hydrogenolysis or by treatment with trifluoroacetic acid.

The removal of such a phenolic hydroxy protecting group may be effected by any of the procedures known for such a transformation, including those reaction conditions indicated in standard texts such as that indicated hereinbefore, or by a related procedure. The reaction conditions preferably being such that the hydroxy derivative is produced without unwanted reactions at other sites within the starting or product compounds. For example, where the protecting group P^1 is acetate, the transformation may conveniently be effected by treatment of the quinazoline derivative with a base as defined hereinbefore and including ammonia, and its mono and di-alkylated derivatives, preferably in the presence of a protic solvent or co-solvent such as water or an alcohol, for example methanol or ethanol. Such a reaction can be effected in the presence of an additional inert solvent or diluent as defined hereinbefore and at a temperature in the range 0 to 50°C, conveniently at about 20°C.

One compound of formula II may if desired be converted into another compound of formula II in which the moiety L^1 is different. Thus for example a compound of formula II in which L^1 is other than halogeno, for example optionally substituted phenoxy, may be converted to a compound of formula II in which L^1 is halogeno by hydrolysis of a compound of formula II (in which L^1 is other than halogeno) to yield a compound of formula X as hereinbefore

defined, followed by introduction of halide to the compound of formula X, thus obtained as hereinbefore defined, to yield a compound of formula II in which L^1 represents halogeno.

(ii) Compounds of the formula IV as hereinbefore defined and salts thereof may be made by deprotecting the compound of formula XVIII:

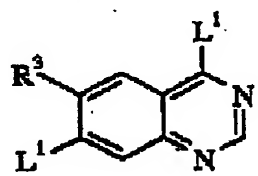


(XVIII)

(wherein R^1, R^3, P^1, X^2 and Z are as hereinbefore defined) by a process for example as described in (i) above.

Compounds of the formula XVIII and salts thereof may be made by reacting compounds of the formulae XVII and III as hereinbefore defined, under the conditions described in (a) hereinbefore, to give a compound of the formula XVIII or salt thereof.

(iii) Compounds of the formula VI and salts thereof as hereinbefore defined may be made by reacting a compound of the formula XIX:



(XIX)

(wherein R^3 and L^1 are as hereinbefore defined, and L^1 in the 4- and 7- positions may be the same or different) with a compound of formual III as hereinbefore defined, the reaction for example being effected by a process as described in (a) above.

(iv) A compound of the formula VIII may be prepared by the reaction of a compound of the formula IV as defined hereinbefore with a compound of the formula XX:

$$R^6\text{-}L^1 \qquad (XX)$$

wherein R^6 and L^1 are as defined hereinbefore under the conditions described in (b) hereinbefore to give a compound of the formula VIII or salt thereof. The reaction is preferably effected in the presence of a base (as defined hereinbefore in process (a)) and advantageously in the presence of an inert solvent or diluent (as defined hereinbefore in process (a)), advantageously at a temperature in the range, for example 10 to 150°C, conveniently in the range 20-50°C.

When a pharmaceutically acceptable salt of a compound of the formula I is required, it may be obtained, for example, by reaction of said compound with, for example, an acid using a conventional procedure, the acid having a pharmaceutically acceptable anion.

Certain of the intermediates herein are novel and these are presented as a further aspect of the present invention.

The identification of compounds which potently inhibit the tyrosine kinase activity associated with the VEGF receptors such as Flt and/or KDR, which inhibit the tyrosine kinase activity associated with the EGF receptor and which are inactive or only weakly active in the hERG assay, is desirable and is the subject of the present invention.

These properties may be assessed, for example, using one or more of the procedures set out below:

(a) *In Vitro* Receptor Tyrosine Kinase Inhibition Test

This assay determines the ability of a test compound to inhibit tyrosine kinase activity. DNA encoding VEGF or epidermal growth factor (EGF) receptor cytoplasmic domains may be obtained by total gene synthesis (Edwards M, International Biotechnology Lab 5(3), 19-25, 1987) or by cloning. These may then be expressed in a suitable expression system to obtain polypeptide with tyrosine kinase activity. For example VEGF and EGF receptor cytoplasmic domains, which were obtained by expression of recombinant protein in insect cells, were found to display intrinsic tyrosine kinase activity. In the case of the VEGF receptor Flt (Genbank accession number X51602), a 1.7kb DNA fragment encoding most of the cytoplasmic domain, commencing with methionine 783 and including the termination codon, described by Shibuya et al (Oncogene, 1990, 5: 519-524), was isolated from cDNA and cloned into a baculovirus transplacement vector (for example pAcYM1 (see The Baculovirus Expression System: A Laboratory Guide, L.A. King and R. D. Possee, Chapman and Hall, 1992) or pAc360 or pBlueBacHis (available from Invitrogen Corporation)). This recombinant construct was co-

transfected into insect cells (for example Spodoptera frugiperda 21(Sf21)) with viral DNA (eg Pharmingen BaculoGold) to prepare recombinant baculovirus. (Details of the methods for the assembly of recombinant DNA molecules and the preparation and use of recombinant baculovirus can be found in standard texts for example Sambrook et al, 1989, Molecular cloning - A Laboratory Manual, 2nd edition, Cold Spring Harbour Laboratory Press and O'Reilly et al, 1992, Baculovirus Expression Vectors - A Laboratory Manual, W. H. Freeman and Co, New York). For other tyrosine kinases for use in assays, cytoplasmic fragments starting from methionine 806 (KDR, Genbank accession number L04947) and methionine 668 (EGF receptor, Genbank accession number X00588) may be cloned and expressed in a similar manner.

For expression of cFlt tyrosine kinase activity, Sf21 cells were infected with plaque-pure cFlt recombinant virus at a multiplicity of infection of 3 and harvested 48 hours later. Harvested cells were washed with ice cold phosphate buffered saline solution (PBS) (10mM sodium phosphate pH7.4, 138mM sodium chloride, 2.7mM potassium chloride) then resuspended in ice cold HNTG/PMSF (20mM Hepes pH7.5, 150mM sodium chloride, 10% v/v glycerol, 1% v/v Triton X100, 1.5mM magnesium chloride, 1mM ethylene glycol-bis(βaminoethyl ether) N,N,N',N'-tetraacetic acid (EGTA), 1mM PMSF (phenylmethylsulphonyl fluoride); the PMSF is added just before use from a freshly-prepared 100mM solution in methanol) using 1ml HNTG/PMSF per 10 million cells. The suspension was centrifuged for 10 minutes at 13,000 rpm at 4°C, the supernatant (enzyme stock) was removed and stored in aliquots at -70°C. Each new batch of stock enzyme was titrated in the assay by dilution with enzyme diluent (100mM Hepes pH 7.4, 0.2mM sodium orthovanadate, 0.1% v/v Triton X100, 0.2mM dithiothreitol). For a typical batch, stock enzyme is diluted 1 in 2000 with enzyme diluent and 50μl of dilute enzyme is used for each assay well.

A stock of substrate solution was prepared from a random copolymer containing tyrosine, for example Poly (Glu, Ala, Tyr) 6:3:1 (Sigma P3899), stored as 1 mg/ml stock in PBS at -20°C and diluted 1 in 500 with PBS for plate coating.

On the day before the assay 100μl of diluted substrate solution was dispensed into all wells of assay plates (Nunc maxisorp 96-well immunoplates) which were sealed and left overnight at 4°C.

On the day of the assay the substrate solution was discarded and the assay plate wells were washed once with PBST (PBS containing 0.05% v/v Tween 20) and once with 50mM Hepes pH7.4.

Test compounds were diluted with 10% dimethylsulphoxide (DMSO) and 25μl of diluted compound was transferred to wells in the washed assay plates. "Total" control wells contained 10% DMSO instead of compound. Twenty five microlitres of 40mM manganese(II)chloride containing 8μM adenosine-5'-triphosphate (ATP) was added to all test wells except "blank" control wells which contained manganese(II)chloride without ATP. To start the reactions 50μl of freshly diluted enzyme was added to each well and the plates were incubated at room temperature for 20 minutes. The liquid was then discarded and the wells were washed twice with PBST. One hundred microlitres of mouse IgG anti-phosphotyrosine antibody (Upstate Biotechnology Inc. product 05-321), diluted 1 in 6000 with PBST containing 0.5% w/v bovine serum albumin (BSA), was added to each well and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with PBST. One hundred microlitres of horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham product NXA 931), diluted 1 in 500 with PBST containing 0.5% w/v BSA, was added and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with PBST. One hundred microlitres of 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) solution, freshly prepared using one 50mg ABTS tablet (Boehringer 1204 521) in 50ml freshly prepared 50mM phosphate-citrate buffer pH5.0 + 0.03% sodium perborate (made with 1 phosphate citrate buffer with sodium perborate (PCSB) capsule (Sigma P4922) per 100ml distilled water), was added to each well. Plates were then incubated for 20-60 minutes at room temperature until the optical density value of the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibtion of enzyme activity.

<u>(b) *In Vitro* HUVEC Proliferation Assay</u>

This assay determines the ability of a test compound to inhibit the growth factor-stimulated proliferation of human umbilical vein endothelial cells (HUVEC).

HUVEC cells were isolated in MCDB 131 (Gibco BRL) + 7.5% v/v foetal calf serum (FCS) and were plated out (at passage 2 to 8), in MCDB 131 + 2% v/v FCS + 3μg/ml heparin + 1μg/ml hydrocortisone, at a concentration of 1000 cells/well in 96 well plates. After a minimum of 4 hours they were dosed with the appropriate growth factor (i.e. VEGF 3ng/ml, EGF 3ng/ml or b-FGF 0.3ng/ml) and compound. The cultures were then incubated for 4 days at 37°C with 7.5% carbon dioxide. On day 4 the cultures were pulsed with 1μCi/well of tritiated-thymidine (Amersham product TRA 61) and incubated for 4 hours. The cells were

harvested using a 96-well plate harvester (Tomtek) and then assayed for incorporation of tritium with a Beta plate counter. Incorporation of radioactivity into cells, expressed as cpm, was used to measure inhibition of growth factor-stimulated cell proliferation by compounds.

(c) *In Vivo* Solid Tumour Disease Model

This test measures the capacity of compounds to inhibit solid tumour growth.

CaLu-6 tumour xenografts were established in the flank of female athymic Swiss nu/nu mice, by subcutaneous injection of $1x10^6$ CaLu-6 cells/mouse in 100μl of a 50% (v/v) solution of Matrigel in serum free culture medium. Ten days after cellular implant, mice were allocated to groups of 8-10, so as to achieve comparable group mean volumes. Tumours were measured using vernier calipers and volumes were calculated as: $(l \times w) \times \sqrt{(l \times w)} \times (\pi/6)$, where l is the longest diameter and w the diameter perpendicular to the longest diameter. Test compounds were administered orally once daily for a minimum of 21 days, and control animals received compound diluent. Tumours were measured twice weekly. The level of growth inhibition was calculated by comparison of the mean tumour volume of the control group versus the treatment group, and statistical significance determined using a Students' t-test and/or a Mann-Whitney Rank Sum Test. The inhibitory effect of compound treatment was considered significant when $p<0.05$.

(d) hERG-encoded Potassium Channel Inhibition Test

This assay determines the ability of a test compound to inhibit the tail current flowing through the human ether-a-go-go-related-gene (hERG)-encoded potassium channel.

Human embryonic kidney (HEK) cells expressing the hERG-encoded channel were grown in Minimum Essential Medium Eagle (EMEM; Sigma-Aldrich catalogue number M2279), supplemented with 10% Foetal Calf Serum (Labtech International; product number 4-101-500), 10% M1 serum-free supplement (Egg Technologies; product number 70916) and 0.4 mg/ml Geneticin G418 (Sigma-Aldrich; catalogue number G7034). One or two days before each experiment, the cells were detached from the tissue culture flasks with Accutase (TCS Biologicals) using standard tissue culture methods. They were then put onto glass coverslips resting in wells of a 12 well plate and covered with 2 ml of the growing media.

For each cell recorded, a glass coverslip containing the cells was placed at the bottom of a Perspex chamber containing bath solution (see below) at ambient temperature (~20 °C). This chamber was fixed to the stage of an inverted, phase-contrast microscope. Immediately after placing the coverslip in the chamber, bath solution was perfused into the chamber from a

gravity-fed reservoir for 2 minutes at a rate of ~ 2 ml/min. After this time, perfusion was stopped.

A patch pipette made from borosilicate glass tubing (GC120F, Harvard Apparatus) using a P-97 micropipette puller (Sutter Instrument Co.) was filled with pipette solution (see hereinafter). The pipette was connected to the headstage of the patch clamp amplifier (Axopatch 200B, Axon Instruments) via a silver/silver chloride wire. The headstage ground was connected to the earth electrode. This consisted of a silver/silver chloride wire embedded in 3% agar made up with 0.85% sodium chloride.

The cell was recorded in the whole cell configuration of the patch clamp technique. Following "break-in", which was done at a holding potential of −80 mV (set by the amplifier), and appropriate adjustment of series resistance and capacitance controls, electrophysiology software (*Clampex*, Axon Instruments) was used to set a holding potential (-80 mV) and to deliver a voltage protocol. This protocol was applied every 15 seconds and consisted of a 1 s step to +40 mV followed by a 1 s step to −50 mV. The current response to each imposed voltage protocol was low pass filtered by the amplifier at 1 kHz. The filtered signal was then acquired, on line, by digitising this analogue signal from the amplifier with an analogue to digital converter. The digitised signal was then captured on a computer running *Clampex* software (Axon Instruments). During the holding potential and the step to + 40 mV the current was sampled at 1 kHz. The sampling rate was then set to 5 kHz for the remainder of the voltage protocol.

The compositions, pH and osmolarity of the bath and pipette solution are tabulated below.

Salt	Pipette (mM)	Bath (mM)
NaCl	-	137
KCl	130	4
$MgCl_2$	1	1
$CaCl_2$	-	1.8
HEPES	10	10
glucose	-	10
Na_2ATP	5	-
EGTA	5	-

Parameter	Pipette	Bath
pH	7.18 – 7.22	7.40
pH adjustment with	1M KOH	1M NaOH
Osmolarity (mOsm)	275-285	285-295

The amplitude of the hERG-encoded potassium channel tail current following the step from +40 mV to –50 mV was recorded on-line by *Clampex* software (Axon Instruments). Following stabilisation of the tail current amplitude, bath solution containing the vehicle for the test substance was applied to the cell. Providing the vehicle application had no significant effect on tail current amplitude, a cumulative concentration effect curve to the compound was then constructed.

The effect of each concentration of test compound was quantified by expressing the tail current amplitude in the presence of a given concentration of test compound as a percentage of that in the presence of vehicle.

Test compound potency (IC_{50}) was determined by fitting the percentage inhibition values making up the concentration-effect to a four parameter Hill equation using a standard data-fitting package. If the level of inhibition seen at the highest test concentration did not exceed 50%, no potency value was produced and a percentage inhibition value at that concentration was quoted.

Although the pharmacological properties of the compounds of formula I vary with structural change, in general, activity possessed by compounds of the formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b) and (c)

Test (a):- IC_{50} in the range, for example, < 5μM;

Test (b):- IC_{50} in the range, for example, 0.001 - 5μM;

Test (c):- activity in the range, for example, 0.1-100mg/kg;

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula I as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier.

The composition may be in a form suitable for oral administration, (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely

divided powder), for parenteral injection (for example as a sterile solution, suspension or emulsion for intravenous, subcutaneous, intramuscular, intravascular or infusion dosing), for topical administration (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), or for rectal administration (for example as a suppository). In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compositions of the present invention are advantageously presented in unit dosage form. The compound will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000mg per square metre body area of the animal, i.e. approximately 0.1-100mg/kg. A unit dose in the range, for example, 1-100mg/kg, preferably 1-50mg/kg is envisaged and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250mg of active ingredient.

According to a further aspect of the present invention there is provided a compound of the formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

A further feature of the present invention is a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament, conveniently a compound of formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method for producing an antiangiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinbefore.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 0.1-50mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity

of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the antiangiogenic and/or vascular permeability reducing treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) other antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], and those that work by different mechanisms from those defined hereinbefore (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function, angiostatin, razoxin, thalidomide), and including vascular targeting agents (for example combretastatin phosphate and compounds disclosed in International Patent Applications WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213 and the vascular damaging agents described in International Patent Application Publication No. WO 99/02166 the entire disclosure of which document is incorporated herein by reference, (for example N-acetylcolchinol-O-phosphate));

(ii) cytostatic agents such as antioestrogens (for example tamoxifen,toremifene, raloxifene, droloxifene, iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide, buserelin), inhibitors of 5α-reductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor), such inhibitors include growth factor antibodies, growth factor receptor antibodies, (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]), farnesyl transferase inhibitors, tyrosine kinase

inhibitors for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)) and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, tegafur, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine, vinorelbine, and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, camptothecin and also irinotecan); also enzymes (for example asparaginase); and thymidylate synthase inhibitors (for example raltitrexed);

and additional types of chemotherapeutic agent include:

(iv) biological response modifiers (for example interferon);

(v) antibodies (for example edrecolomab);

(vi) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(vii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(viii) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as

cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

For example such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of a compound of formula I as defined hereinbefore, and a vascular targeting agent described in WO 99/02166 such as N-acetylcolchinol-O-phosphate (Example 1 of WO 99/02166).

It is known from WO 01/74360 that antiangiogenics can be combined with antihypertensives. A compound of the present invention can also be administered in combination with an antihypertensive. An antihypertensive is an agent which lowers blood pressure, see WO 01/74360 which is incorporated herein by reference.

Thus according to the present invention there is provided a method of treatment of a disease state associated with angiogenesis which comprises the administration of an effective amount of a combination of a compound of the present invention or a pharmaceutically acceptable salt thereof and an anti-hypertensive agent to a warm-blooded animal, such as a human being.

According to a further feature of the present invention there is provided the use of a combination of a compound of the present invention or a pharmaceutically acceptable salt thereof and an anti-hypertensive agent for use in the manufacture of a medicament for the treatment of a disease state associated with angiogenesis in a warm-blooded mammal, such as a human being.

According to a further feature of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention or a pharmaceutically acceptable salt thereof and an anti-hypertensive agent for the treatment of a disease state associated with angiogenesis in a warm-blooded mammal, such as a human being.

According to a further aspect of the present invention there is provided a method for producing an anti-angiogenic and/or vascular permeability reducing effect in a warm-blooded animal, such as a human being, which comprises administering to said animal an effective amount of a combination of a compound of the present invention or a pharmaceutically acceptable salt thereof and an anti-hypertensive agent.

According to a further aspect of the present invention there is provided the use of a combination of a compound of the present invention or a pharmaceutically acceptable salt thereof and an anti-hypertensive agent for the manufacture of a medicament for producing an

anti-angiogenic and/or vascular permeability reducing effect in a warm-blooded mammal, such as a human being.

Preferred antihypertensive agents are calcium channel blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists (A-II antagonists), diuretics, beta-adrenergic receptor blockers (β-blockers), vasodilators and alpha-adrenergic receptor blockers (α-blockers). Particular antihypertensive agents are calcium channel blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists (A-II antagonists) and beta-adrenergic receptor blockers (β-blockers), especially calcium channel blockers.

As stated above the compounds defined in the present invention are of interest for their antiangiogenic and/or vascular permeability reducing effects. Such compounds of the invention are expected to be useful in a wide range of disease states including cancer, diabetes, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, lymphoedema, acute and chronic nephropathies, atheroma, arterial restenosis, autoimmune diseases, acute inflammation, excessive scar formation and adhesions, endometriosis, dysfunctional uterine bleeding and ocular diseases with retinal vessel proliferation including age-related macular degeneration. Cancer may affect any tissue and includes leukaemia, multiple myeloma and lymphoma. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention are expected to inhibit any form of cancer associated with VEGF including leukaemia, mulitple myeloma and lymphoma and also, for example, the growth of those primary and recurrent solid tumours which are associated with VEGF, especially those tumours which are significantly dependent on VEGF for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

In another aspect of the present invention compounds of formula I are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with EGF especially those tumours which are significantly dependent on EGF for their growth and spread.

In another aspect of the present invention compounds of formula I are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with both VEGF and EGF especially those tumours which are significantly dependent on VEGF and EGF for their growth and spread, for example non-small cell lung cancer (NSCLC).

In addition to their use in therapeutic medicine, the compounds of formula I and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of in vitro and in vivo test systems for the evaluation of the effects of inhibitors of VEGF receptor tyrosine kinase activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

It is to be understood that where the term "ether" is used anywhere in this specification it refers to diethyl ether.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

(i) evaporations were carried out by rotary evaporation <u>in vacuo</u> and work-up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Koffler hot plate apparatus.

(vi) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(viii) HPLC were run under 2 different conditions:

1) on a TSK Gel super ODS 2μM 4.6mm x 5cm column, eluting with a gradient of methanol in water (containing 1% acetic acid) 20 to 100% in 5 minutes. Flow rate 1.4 ml/minute. Detection: U.V. at 254 nm and light scattering detections;

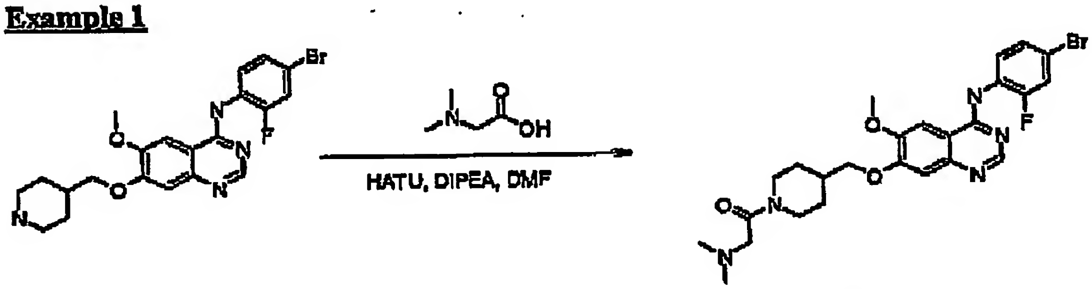
2) on a TSK Gel super ODS 2μM 4.6mm x 5cm column, eluting with a gradient of methanol in water (containing 1% acetic acid) 0 to 100% in 7 minutes. Flow rate 1.4 ml/minute. Detection: U.V. at 254 nm and light scattering detections.

(ix) petroleum ether refers to that fraction boiling between 40-60°C

(x) the following abbreviations have been used:-

DMF N,N-dimethylformamide
DMSO dimethylsulphoxide
TFA trifluoroacetic acid
THF tetrahydrofuran
LC-MS HPLC coupled to mass spectrometry

Example 1



4-(4-Bromo-2-fluoroanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline (0.9g, 1.95mmol), *O*-(7-azabenzotriazol-1-yl)-*N, N, N', N'*-tetramethyluronium hexafluorophosphate (0.89g, 2.34mmol) and *N,N*-dimethylglycine (241mg, 2.34mmol) were dissolved in *N,N*-dimethylformamide (10ml) and diisopropylethylamine (0.68ml, 3.90mmol) was added. The reaction mixture was stirred at room temperature for 3 hours, diluted with ethyl acetate, washed with brine, 2N sodium hydroxide, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue (2.5% 7N ammonia in methanol/dichloromethane) gave **4-(4-bromo-2-fluoroanilino)-7-({1-[(*N,N*-dimethylamino)acetyl]piperidin-4-yl}methoxy)-6-methoxyquinazoline** (750mg, 70%) as a white solid.

LC-MS (ESI) 548.0 [M(^{81}Br) H]$^+$

^{1}H NMR (spectrum): (DMSOd$_6$) 1.17-1.35 (m, 2H); 1.83 (br d, 2H); 2.11 (m, 1H); 2.19 (s, 6H); 2.62 (br t, 1H); 3.02 (m, 2H); 3.12 (d, 1H); 3.95 (s, 3H); 4.03 (d, 2H); 4.10 (br d, 1H); 4.40 (br d, 1H); 7.20 (s, 1H); 7.47 (dd, 1H); 7.59 (m, 1H); 7.65 (dd, 1H); 7.80 (s, 1H); 8.30 (s, 1H); 9.[illegible]), 1H)

The starting material was prepared as follows:

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (10g, 0.04m[illegible] Chem. 1977, vol 20, 146-149), and Gold's reagent (7.4g, 0.05mol) in di[illegible] (100ml) was stirred and heated at reflux for 24 hours. Sodium acetate (3.02g, 0.037mol) and acetic acid (1.65ml, 0.029mol) were added to the reaction mixture and it was heated for a further 3 hours. The mixture was evaporated, water was added to the residue, the solid was filtered off, washed with water and dried ($MgSO_4$). Recrystallisation from acetic acid gave 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7g, 84%).

10% Palladium on carbon (8.3g) was added to a suspension of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (50 g, 0.177 mol) in dimethylformamide (800 ml) under nitrogen. Ammonium formate (111.8 g, 1.77 mol) was then added in portions over 5 minutes. The reaction mixture was stirred for one hour at ambient temperature then heated to 80°C for a further hour. The reaction mixture was filtered hot through diatomaceous earth and the residues washed with dimethylformamide. The filtrate was then concentrated and the residue suspended in water. The pH was adjusted to 7.0 using 2M sodium hydroxide and the resulting mixture was stirred at ambient temperature for one hour. The solid was filtered, washed with water and dried over phosphorus pentoxide yielding 7-hydroxy-6-methoxy-3,4-dihydroquinazolin-4-one as a white solid (20.52 g, 60%).

^{1}H NMR Spectrum: (DMSOd$_6$) 3.85 (s, 3H), 6.95 (s, 1H), 7.40 (s, 1H), 7.85 (s, 1H)

MS-ESI: 193 [M+H]+

Pyridine (20 ml) was added to a suspension of 7-hydroxy-6-methoxy-3,4-dihydroquinazolin-4-one (20.5 g, 107 mmol) in acetic anhydride (150 ml, 1.6 mol). The reaction mixture was heated to 120°C for three hours, during which time the solid dissolved. The reaction mixture was allowed to cool then poured into ice-water (900 ml). The reaction mixture was stirred for one hour then the solid was removed by filtration and dried over phosphorus pentoxide yielding 7-acetoxy-6-methoxy-3,4-dihydroquinazolin-4-one as a white solid (20.98 g, 84%).

^{1}H NMR Spectrum: (DMSOd$_6$) 2.25 (s, 3H), 3.85 (s, 3H), 7.40 (s, 1H), 7.60 (s, 1H), 8.00 (s, 1H)

MS-ESI: 235 [M+H]+

7-Acetoxy-6-methoxy-3,4-dihydroquinazolin-4-one (1 g, 4.3 mmol) was suspended in thionyl chloride (10.5 ml). One drop of *N,N*-dimethylformamide was added and the reaction was heated to 80°C for two hours, during which time the solid dissolved. The reaction mixture was cooled and the thionyl chloride was removed *in vacuo*. The residue was azeotroped with toluene before being suspended in methylene chloride. A solution of 10% ammonia in methanol (40 ml) was added and the reaction mixture was heated to 80°C for 15 minutes. After cooling the solvents were removed *in vacuo* and the residue redissolved in water (10 ml) and the pH adjusted to 7.0 with 2M hydrochloric acid. The resulting solid was filtered, washed with water and dried over phosphorus pentoxide yielding 4-chloro-7-hydroxy-6-methoxyquinazoline as a white solid (680 mg, 75%).

^{1}H NMR Spectrum: (DMSOd$_6$) 4.00 (s, 3H), 7.25 (s, 1H), 7.35 (s, 1H), 8.75 (s, 1H)

MS-ESI: 211-213 [M+H]+

While maintaining the temperature in the range 0-5°C, a solution of di-*tert*-butyl dicarbonate (41.7g, 0.19mol) in ethyl acetate (75ml) was added in portions to a solution of ethyl 4-piperidinecarboxylate (30g, 0.19mol) in ethyl acetate (150ml) cooled at 5°C. After stirring for 48 hours at ambient temperature, the mixture was poured onto water (300ml). The organic layer was separated, washed successively with water (200ml), 0.1N aqueous hydrochloric acid (200ml), saturated sodium hydrogen carbonate (200ml) and brine (200ml), dried ($MgSO_4$) and evaporated to give ethyl 4-(1-(*tert*-butoxycarbonyl)piperidine)carboxylate (48g, 98%).

^{1}H NMR Spectrum: ($CDCl_3$) 1.25(t, 3H); 1.45(s, 9H); 1.55-1.70(m, 2H); 1.8-2.0(d, 2H); 2.35-2.5(m, 1H); 2.7-2.95(t, 2H); 3.9-4.1(br s, 2H); 4.15 (q, 2H)

A solution of 1M lithium aluminium hydride in THF (133ml, 0.133mol) was added in portions to a solution of ethyl 4-(1-(*tert*-butoxycarbonyl)piperidine)carboxylate (48g, 0.19mol) in dry THF (180ml) cooled at 0°C. After stirring at 0°C for 2 hours, water (30ml) was added followed by 2N sodium hydroxide (10ml). The precipitate was removed by filtration through diatomaceous earth and washed with ethyl acetate. The filtrate was washed with water, brine, dried ($MgSO_4$) and evaporated to give 1-(*tert*-butoxycarbonyl)-4-hydroxymethylpiperidine (36.3g, 89%).

MS (EI): 215 [M.]+

^{1}H NMR Spectrum: ($CDCl_3$) 1.05-1.2(m, 2H); 1.35-1.55(m, 10H); 1.6-1.8(m, 2H); 2.6-2.8(t, 2H); 3.4-3.6(t, 2H); 4.0-4.2(br s, 2H)

4-Chloro-7-hydroxy-6-methoxyquinazoline (1.5g, 7.12mmol), *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (also known as 1-(*tert*-butoxycarbonyl)-4-hydroxymethylpiperidine) (1.8g, 8.55mmol) and triphenylphosphine (2.2g, 8.55mmol) were stirred in dichloromethane (30ml) and cooled in an ice/water bath. Diisopropyl azodicarboxylate (1.7ml, 8.55mmol) was slowly added and the mixture stirred at room temperature for 3 hours before being concentrated under reduced pressure. Column chromatography of the residue (2:1 isohexane/ethyl acetate) gave *tert*-butyl 4-{[(4-chloro-6-methoxyquinazolin-7-yl)oxy]methyl}piperidine-1-carboxylate (2.1g, 72%) as a white solid.

LC-MS (ESI) 408.1 and 410.1 $[MH]^+$

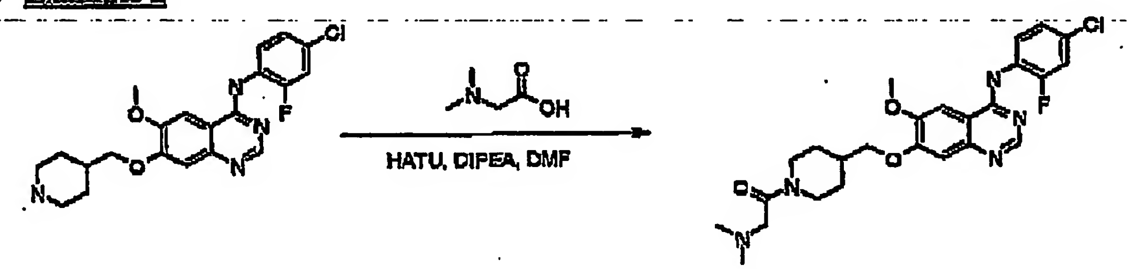
^{1}H NMR (spectrum): (DMSOd_6) 1.33 (m, 2H); 1.52 (s, 9H); 1.90 (d, 2H); 2.16 (m, 1H); 2.89 (m, 2H); 4.11 (m, 5H); 4.22 (d, 2H); 7.50 (s, 1H); 7.55 (s, 1H); 8.98 (s, 1H)

tert-Butyl 4-{[(4-chloro-6-methoxyquinazolin-7-yl)oxy]methyl}piperidine-1-carboxylate (1.0g, 2.45mmol) and 4-bromo-2-fluoroaniline (0.56g, 2.94mmol) were stirred in 2-propanol (30ml) and hydrogen chloride (0.74ml of a 4M solution in dioxane, 2.94mmol) was added. The mixture was heated at reflux for 4 hours, cooled and filtered. The solid was dissolved in methanol, placed on an Isolute® SCX column, washed with methanol and then eluted with 7N ammonia in methanol to give 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline (920mg, 81%) as a pale brown foam.

LC-MS (ESI) 463.0 $[M(^{81}Br)H]^+$

^{1}H NMR (spectrum): (DMSOd_6) 1.41 (m, 2H); 1.89 (d, 2H); 2.08 (m, 1H); 2.71 (t, 2H); 3.16 (d, 2H); 4.06 (m, 5H); 7.30 (s, 1H); 7.62 (m, 2H); 7.17 (d, 1H); 7.93 (s, 1H); 8.46 (s, 1H); 9.68 (br s, 1H)

Example 2



4-(4-Chloro-2-fluoroanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline (1.0g, 2.40mmol), *O*-(7-azabenzotriazol-1-yl)-*N, N, N', N'*-tetramethyluronium hexafluorophosphate (1.09g, 2.88mmol) and *N,N*-dimethylglycine (297mg, 2.88mmol) were dissolved in *N,N*-

dimethylformamide (10ml) and diisopropylethylamine (0.84ml, 4.80mmol) was added. The reaction mixture was stirred at room temperature for 3 hours, diluted with ethyl acetate, washed with brine, 2N sodium hydroxide, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue (2.5% 7N ammonia in methanol/dichloromethane) gave **4-(4-chloro-2-fluoroanilino)-7-({1-[(*N,N*-dimethylamino)acetyl]piperidin-4-yl}methoxy)-6-methoxyquinazoline** (940mg, 78%) as a white solid.

LC-MS (ESI) 502.1 and 504.1 $[MH]^+$

^1H NMR (spectrum): ($DMSOd_6$) 1.17-1.35 (m, 2H); 1.83 (br d, 2H); 2.11 (m, 1H); 2.19 (s, 6H); 2.62 (br t, 1H); 3.04 (m, 2H); 3.13 (d, 1H); 3.95 (s, 3H); 4.03 (d, 2H); 4.08 (br d, 1H); 4.40 (br d. 1H); 7.20 (s, 1H); 7.35 (m, 1H); 7.54 (dd, 1H); 7.59 (m, 1H); 7.80 (s, 1H); 8.36 (s, 1H); 9.51 (s, 1H)

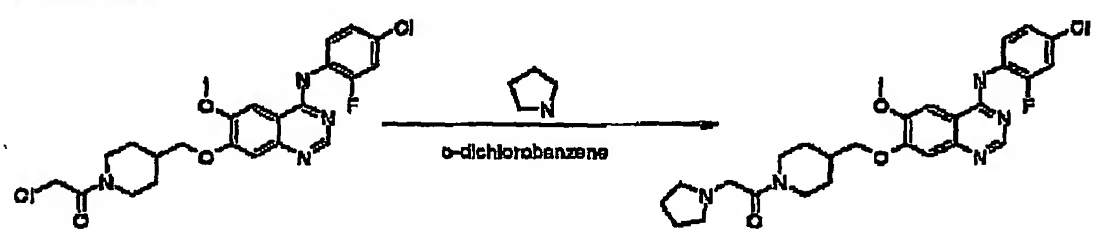
The starting material was prepared as follows:

tert-Butyl 4-{[(4-chloro-6-methoxyquinazolin-7-yl)oxy]methyl}piperidine-1-carboxylate (1.0g, 2.45mmol), (prepared as described for the starting material in Example 1), and 4-chloro-2-fluoroaniline (0.33ml, 2.94mmol) were stirred in 2-propanol (30ml) and hydrogen chloride (0.74ml of a 4M solution in dioxane, 2.94mmol) was added. The mixture was heated at reflux for 4 hours, cooled and filtered. The solid was dissolved in methanol, placed on an Isolute® SCX column, washed with methanol and then eluted with 7N ammonia in methanol to give 4-(4-chloro-2-fluoroanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline (1.0g, 98%) as a white solid.

LC-MS (ESI) 417.1 and 419.1 $[MH]^+$

^1H NMR (spectrum): ($DMSOd_6$) 1.47 (m, 2H); 1.93 (d, 2H); 2.13 (m, 1H); 2.78 (t, 2H); 3.20 (d, 2H); 4.06 (m, 5H); 7.31 (s, 1H); 7.45 (m, 1H); 7.67 (m, 2H); 7.95 (s, 1H); 8.46 (s, 1H); 9.73 (br s, 1H)

<u>Example 3</u>



7-{[1-(Chloroacetyl)piperidin-4-yl]methoxy}-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline (150mg, 0.30mmol) was suspended in *O*-dichlorobenzene (3ml) and pyrrolidine (63µl, 0.76mmol) added. The mixture was heated at 120°C for 1.5 hours. The reaction mixture was cooled and placed directly onto a silica column, washed with dichloromethane to remove the *O*-dichlorobenzene and then eluted with 2% 7N ammonia in methanol/dichloromethane to give **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-{[1-(pyrrolidin-1-ylacetyl)piperidin-4-yl]methoxy}quinazoline** (115mg, 72%).

LC-MS (ESI) 528.1 and 530.1 $[MH]^+$

^1H NMR (spectrum): ($DMSOd_6$) 1.25 (m, 2H); 1.69 (m, 4H); 1.82 (br d, 2H); 2.11 (m, 1H); 2.50 (m, 4H); 2.61 (br t, 1H); 3.03 (br t, 1H); 3.17 (d, 1H); 3.34 (d, 1H); 3.95 (s, 3H); 4.06 (m, 3H); 4.39 (br d, 1H); 7.20 (s, 1H); 7.34 (m, 1H); 7.54 (dd, 1H); 7.59 (t, 1H); 7.80 (s, 1H); 8.35 (s, 1H); 9.51 (s, 1H)

The starting material was prepared as follows:

4-(4-Chloro-2-fluoroanilino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline (2.2g, 4.85mmol) (prepared as described for the starting material in Example 2) was suspended in methylene chloride (100ml) and diisopropylethylamine (2.1ml, 12.1mmol) was added. Chloroacetyl chloride (0.4ml, 5.34mmol) was slowly added and the mixture stirred at room temperature for 2 hours. A further 0.5 equivalents of chloroacetyl chloride and diisopropylethylamine were added and the reaction mixture stirred for a further 2 hours. The mixture was washed with 2N hydrochloric acid, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue (2%-5%-7% methanol/dichloromethane) gave 7-{[1-(chloroacetyl)piperidin-4-yl]methoxy}-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline (1.52g, 62%) as a brown solid.

LC-MS (ESI) 493, 495 and 496.1 $[MH]^+$

^1H NMR (spectrum): ($DMSOd_6$) 1.15-1.30 (m, 2H); 1.96 (d, 2H); 2.15 (m, 1H); 2.72 (m, 1H); 3.14 (m, 1H); 3.90 (d, 1H); 3.97 (s, 3H); 4.06 (d, 2H); 4.39 (m, 3H); 7.23 (s, 1H); 7.46 (m, 1H); 7.72 (m, 2H); 7.89 (s, 1H); 8.42 (s, 1H); 9.84 (br s, 1H)

Examples 4-11

Using an analogous procedure to that described in the preparation of Example 3, 7-{[1-(chloroacetyl)piperidin-4-yl]methoxy}-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline was reacted with the appropriate amine to give the compounds described in Table 1.

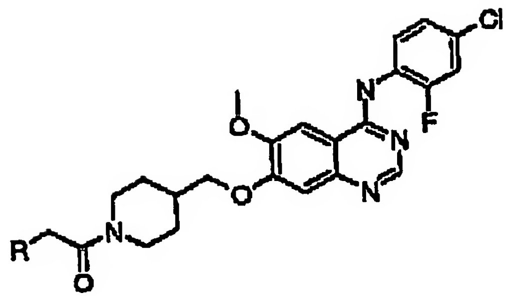
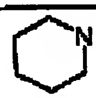
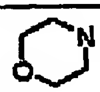
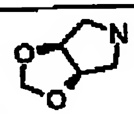
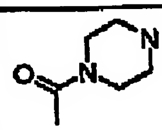
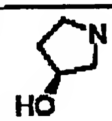
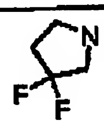


Table 1

Example number	R	note
4		1)
5		2)
6		3)
7		4)
8		5)
9		6)
10	Me NH	7)
11		8)

Notes

1) 4-(4-chloro-2-fluoroanilino)-6-methoxy-7-{[1-(piperidin-1-ylacetyl)piperidin-4-yl]methoxy}quinazoline (95mg, 58%)

LC-MS (ESI) 542.1 and 544.1 $[MH]^+$

^{1}H NMR (spectrum): (DMSOd$_6$) 1.18 (m, 1H); 1.37 (m, 3H); 1.50 (m, 4H); 1.83 (m, 2H); 2.12 (m, 1H); 2.35 (m, 4H); 2.62 (m, 1H); 3.06 (m, 2H); 3.20 (m, 1H); 3.95 (s, 3H); 4.04 (d, 2H); 4.14 (d, 1H); 4.39 (d, 1H); 7.20 (s, 1H); 7.35 (d, 1H); 7.57 (m, 2H); 7.80 (s, 1H); 8.35 (s, 1H); 9.51 (s, 1H)

2) **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-{[1-(morpholin-4-ylacetyl)piperidin-4-yl]methoxy}quinazoline** (98mg, 59%)

LC-MS (ESI) 544.1 and 546.1 [MH]$^+$

^{1}H NMR (spectrum): (DMSOd$_6$) 1.19 (m, 1H); 1.36 (m, 1H); 1.84 (m, 2H); 2.12 (m, 1H); 2.41 (m, 4H); 2.63 (m, 1H); 3.06 (m, 2H); 3.27 (d, 1H); 3.58 (m, 4H); 3.95 (s, 3H); 4.04 (d, 2H); 4.10 (d, 1H); 4.39 (d, 1H); 7.20 (s, 1H); 7.35 (d, 1H); 7.54 (dd, 1H); 7.59 (t, 1H); 7.80 (s, 1H); 8.36 (s, 1H); 9.51 (s, 1H)

3) **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-({1-[(3a*R*,6a*S*)-tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-ylacetyl]piperidin-4-yl}methoxy)quinazoline** (61mg, 35%)

LC-MS (ESI) 572.0 and 574.1 [MH]$^+$

^{1}H NMR (spectrum): (DMSOd$_6$) 1.17 (m, 1H); 1.32 (m, 1H); 1.83 (d, 2H); 2.11 (m, 1H); 2.24 (d, 2H); 2.63 (m, 1H); 3.00 (m, 3H); 3.13 (d, 1H); 3.27 (d, 1H); 3.95 (s, 3H); 4.04 (m, 3H); 4.38 (d, 1H); 4.57 (s, 2H); 4.89 (s, 1H); 4.95 (s, 1H); 7.20 (s, 1H); 7.35 (d, 1H); 7.54 (dd, 1H); 7.59 (t, 1H); 7.80 (s, 1H); 8.35 (s, 1H); 9.52 (s, 1H)

The (3RS,4SR)-3,4-methylenedioxypyrrolidine used as a starting material was prepared as follows :-

A solution of di-tert-butyl dicarbonate (Boc$_2$O, 78.95 g) in ethyl acetate (125 ml) was added dropwise to a stirred mixture of 3-pyrroline (25 g; 65% pure containing pyrrolidine) and ethyl acetate (125 ml) which had been cooled to 0°C. The reaction temperature was maintained at 5-10°C during the addition. The resultant reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was washed successively with water, 0.1N aqueous hydrochloric acid solution, water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. There was thus obtained, as a colorless oil (62 g), a 2:1 mixture of *tert*-butyl 3-pyrroline-1-carboxylate, ^{1}H NMR (spectrum): (CDCl$_3$) 1.45 (s, 9H), 4.1 (d, 4H), 6.75 (m, 2H), and tert-butyl pyrrolidine-1-carboxylate, ^{1}H NMR (spectrum): (CDCl$_3$) 1.5 (s, 9H), 1.8 (br s, 4H), 3.3 (br s, 4H).

A solution of the mixture of materials so obtained in acetone (500 ml) was added dropwise to a mixture of *N*-methylmorpholine-*N*-oxide (28.45 g), osmium tetroxide (1 g) and water (500 ml) whilst keeping the reaction temperature below 25°C. The reaction mixture was then stirred at ambient temperature for 5 hours. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent and by further column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol. There was thus obtained *tert*-butyl (3RS,4SR)-3,4-dihydroxypyrrolidine-1-carboxylate as an oil (34.6 g).

^{1}H NMR (spectrum): ($CDCl_3$) 1.45 (s, 9H), 2.65 (m, 2H), 3.35 (m, 2H), 3.6 (m, 2H), 4.25 (m, 2H).

A solution of *tert*-butyl (3RS,4SR)-3,4-dihydroxypyrrolidine-1-carboxylate (34.6 g) in DMF (400 ml) was cooled to 0-5°C and sodium hydride (60% dispersion in mineral oil, 0.375 mol) was added portionwise. The reaction mixture was stirred at 5°C for 1 hour. Dibromomethane (15.6 ml) was added and the reaction mixture was stirred at 5°C for 30 minutes. The reaction mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The DMF was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained *tert*-butyl (3RS,4SR)-3,4-methylenedioxypyrrolidine-1-carboxylate as a colourless oil (19.77 g).

^{1}H NMR (spectrum): ($CDCl_3$) 1.45 (s, 9H), 3.35 (m, 2H), 3.75 (br s, 2H), 4.65 (m, 2H), 4.9 (s, 1H), 5.1 (s, 1H).

A cooled 5M solution of hydrogen chloride in isopropanol (150 ml) was added to a solution of *tert*-butyl (3RS,4SR)-3,4-methylenedioxypyrrolidine-1-carboxylate (19.7 g) in methylene chloride (500 ml) that was cooled in an ice bath. The reaction mixture was allowed to warm to ambient temperature and was stirred for 4 hours. The solvent was evaporated and the residue was triturated under diethyl ether. The precipitate was collected by filtration, washed with diethyl ether and dried. There was thus obtained (3RS,4SR)-3,4-methylenedioxypyrrolidine hydrochloride as a beige solid (13.18 g).

^{1}H NMR (spectrum): (DMSOd$_6$) 3.15 (m, 2H), 3.35 (m, 2H), 4.65 (s, 1H), 4.8 (m, 2H), 5.1 (s, 1H).

The material so obtained was suspended in diethyl ether and a saturated methanolic ammonia solution was added. The resultant mixture was stirred at ambient temperature for 10 minutes. The mixture was filtered and the solvent was evaporated at ambient temperature under vacuum. There was thus obtained (3RS,4SR)-3,4-methylenedioxypyrrolidine which was used without any additional purification.

4) **7-({1-[(4-acetylpiperazin-1-yl)acetyl]piperidin-4-yl}methoxy)-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline (70mg, 39%)**

LC-MS (ESI) 585 and 587 [MH]$^+$

^{1}H NMR (spectrum): (DMSOd$_6$) 1.20 (m, 1H); 1.35 (m, 1H); 1.84 (m, 2H); 1.98 (s, 3H); 2.12 (m, 1H); 2.37 (m, 2H); 2.43 (m, 2H); 2.63 (m, 1H); 3.08 (m, 2H); 3.30 (d, 1H); 3.42 (m, 4H); 3.95 (s, 3H); 4.05 (m, 3H); 4.39 (d, 1H); 7.20 (s, 1H); 7.35 (d, 1H); 7.54 (dd, 1H); 7.59 (t, 1H); 7.79 (s, 1H); 8.35 (s, 1H); 9.51 (s, 1H)

5) **(3*S*)-7-({1-[(3-hydroxypyrrolidin-1-yl)acetyl]piperidin-4-yl}methoxy)-4-(4-chloro-2-fluoroanilino)-6-methoxyquinazoline (34mg, 20%)**

LC-MS (ESI) 543.9 and 546.0 [MH]$^+$

^{1}H NMR (spectrum): (DMSOd$_6$) 1.18 (m, 1H); 1.32 (m, 1H); 1.55 (m, 1H); 1.83 (d, 2H); 1.96 (m, 1H); 2.11 (m, 1H); 2.34 (m, 1H); 2.50 (m, 1H); 2.61 (m, 2H); 2.77 (m, 1H); 3.02 (br t, 1H); 3.17 (dd, 1H); 3.30 (dd, 1H); 3.95 (s, 3H); 4.04 (m, 3H); 4.18 (m, 1H); 4.38 (d, 1H); 4.65 (d, 1H); 7.20 (s, 1H); 7.35 (d, 1H); 7.54 (dd, 1H); 7.59 (t, 1H); 7.80 (s, 1H); 8.35 (s, 1H); 9.51 (s, 1H)

6) **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-[(1-{[*N*-(2-methoxyethyl)amino]acetyl}piperidin-4-yl)methoxy]quinazoline (65mg, 22%)**

LC-MS (ESI) 532 and 534 [MH]$^+$

^{1}H NMR (spectrum): (DMSOd$_6$) 1.74 (m, 2H); 1.84 (d, 2H); 2.12 (m, 1H); 2.66 (m, 3H); 3.02 (t, 1H); 3.25 (s, 3H); 3.40 (m, 4H); 3.85 (d, 1H); 3.95 (s, 3H); 4.03 (d, 2H); 4.42 (d, 1H); 7.20 (s, 1H); 7.35 (d, 1H); 7.45 (dd, 1H); 7.59 (t, 1H); 7.80 (s, 1H); 8.35 (s, 1H); 9.51 (s, 1H)

7) **4-(4-chloro-2-fluoroanilino)-6-methoxy-7-({1-[(N-methylamino)acetyl]piperidin-4-yl}methoxy)quinazoline** (54mg, 46%)

LC-MS (ESI) 488 and 490 [MH]$^+$

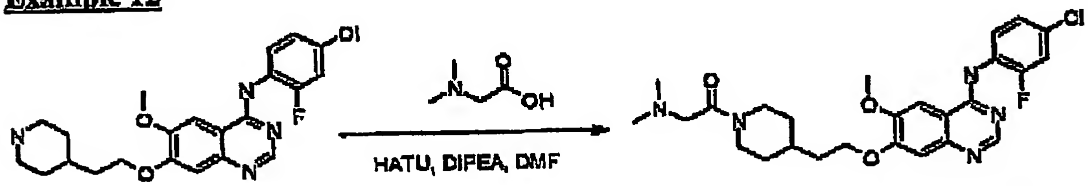
^{1}H NMR (spectrum): (DMSOd$_6$) 1.24 (m, 2H); 1.83 (d, 2H); 2.12 (m, 1H); 2.29 (s, 3H); 2.65 (m, 1H); 3.02 (t, 1H); 3.30 (dd, 2H); 3.86 (d, 1H); 3.95 (s, 3H); 4.03 (d, 2H); 4.42 (d, 1H); 7.20 (s, 1H); 7.35 (d, 1H); 7.57 (m, 2H); 7.80 (s, 1H); 7.36 (s, 1H); 9.52 (s, 1H)

8) **4-(4-chloro-2-fluoroanilino)-7-({1-[(3,3-difluoropyrrolidin-1-yl)acetyl]piperidin-4-yl}methoxy)-6-methoxyquinazoline** (45mg, 26%)

LC-MS (ESI) 586.4 and 570.5 [M+Na]$^+$

^{1}H NMR (spectrum): (DMSOd$_6$) 1.27 (m, 2H); 1.83 (d, 2H); 2.12 (m, 1H); 2.23 (m, 2H); 2.63 (m, 1H); 2.80 (t, 2H); 2.99 (m, 3H); 2.30 (d, 1H); 3.42 (d, 1H); 3.95 (m, 4H); 4.03 (d, 2H); 4.38 (d, 1H); 7.20 (s, 1H); 7.35 (d, 1H); 7.54 (dd, 1H); 7.59 (t, 1H); 7.80 (s, 1H); 8.35 (s, 1H); 9.31 (s, 1H)

<u>Example 12</u>



4-(4-Chloro-2-fluoroanilino)-6-methoxy-7-[2-(piperidin-4-yl)ethoxy]quinazoline (310mg, 0.72mmol), *O*-(7-azabenzotriazol-1-yl)-*N*, *N*, *N'*, *N'*-tetramethyluronium hexafluorophosphate (328mg, 0.86mmol) and *N,N*-dimethylglycine (89mg, 0.86mmol) were dissolved in *N,N*-dimethylformamide (10ml) and diisopropylethylamine (0.25ml, 1.44mmol) was added. The reaction mixture was stirred at room temperature over night, diluted with ethyl acetate, washed with brine (x2), 2N sodium hydroxide, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue (3% 7N ammonia in methanol/dichloromethane) gave **4-(4-chloro-2-fluoroanilino)-7-(2-{1-[(N,N-dimethylamino)acetyl]piperidin-4-yl}ethoxy)-6-methoxyquinazoline** (200mg, 54%) as a white solid.

LC-MS (ESI) 516.1 and 518.1 [MH]$^+$

^{1}H NMR (spectrum): (DMSOd$_6$) 1.03-1.19 (m, 2H); 1.77 (m, 5H); 2.19 (s, 6H); 2.56 (br t, 1H); 2.99 (m, 2H); 3.14 (br d, 1H); 3.95 (s, 3H); 4.02 (br d, 1H); 4.20 (m, 2H); 4.37 (br d,

1H); 7.22 (s, 1H); 7.35 (d, 1H); 7.54 (dd, 1H); 7.59 (t, 1H); 7.80 (s, 1H); 8.36 (s, 1H); 9.51 (s, 1H)

The starting material was prepared as follows:

4-Chloro-7-hydroxy-6-methoxyquinazoline (1.0g, 4.75mmol), (prepared as described for the starting material in Example 1), *tert*-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (1.3g, 5.70mmol) and triphenylphosphine (1.5g, 5.70mmol) were stirred in dichloromethane (25ml) and cooled in an ice/water bath. Diisopropyl azodicarboxylate (1.1ml, 5.70mmol) was slowly added and the mixture stirred at room temperature over night before being concentrated under reduced pressure. Column chromatography of the residue (2:1 isohexane/ethyl acetate) gave a sticky solid which was suspended in diethyl ether and filtered to give *tert*-butyl 4-{2-[(4-chloro-6-methoxyquinazolin-7-yl)oxy]ethyl}piperidine-1-carboxylate (1.4g, 70%) as a white solid.

LC-MS (ESI) 422.0 and 424.0 $[MH]^+$

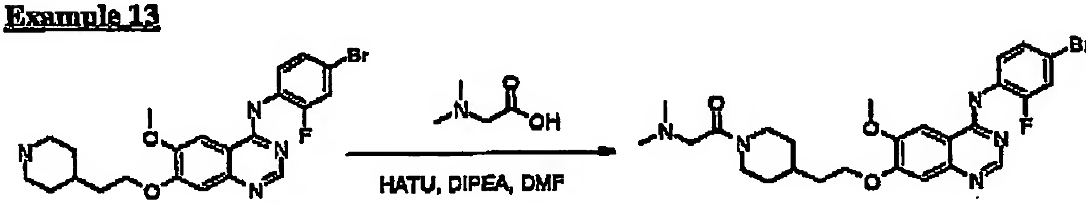
^{1}H NMR (spectrum): (DMSOd_6) 1.09 (m, 2H); 1.40 (s, 9H); 1.77 (m, 5H); 2.72 (m, 2H); 3.93 (br d, 2H); 4.00 (s, 3H); 4.28 (t, 2H); 7.39 (s, 1H); 7.47 (s, 1H); 8.87 (s, 1H)

tert-Butyl 4-{2-[(4-chloro-6-methoxyquinazolin-7-yl)oxy]ethyl}piperidine-1-carboxylate (0.4g, 0.95mmol) and 4-chloro-2-fluoroaniline (126µl, 1.14mmol) were stirred in 2-propanol (15ml) and hydrogen chloride (1.2ml of a 4M solution in dioxane, 4.75mmol) was added. The mixture was heated at reflux for 1.5 hours, cooled and concentrated under reduced pressure. Column chromatography of the residue (10% 7N ammonia in methanol/dichloromethane) gave 4-(4-chloro-2-fluoroanilino)-6-methoxy-7-[2-(piperidin-4-yl)ethoxy]quinazoline (320mg, 75%) as a white solid.

LC-MS (ESI) 431.0 and 433.0 $[MH]^+$

^{1}H NMR (spectrum): (DMSOd_6) 1.09 (m, 2H); 1.57 (m, 1H); 1.69 (m, 4H); 2.45 (dt, 2H); 2.92 (br d, 2H); 3.95 (s, 3H); 4.18 (t, 2H); 7.20 (s, 1H); 7.34 (m, 1H); 7.54 (dd, 1H); 7.59 (t, 1H); 7.79 (s, 1H); 8.35 (s, 1H); 9.52 (br s, 1H)

__Example 13__



4-(4-Bromo-2-fluoroanilino)-6-methoxy-7-[2-(piperidin-4-yl)ethoxy]quinazoline (330mg, 6.94mmol), *O*-(7-azabenzotriazol-1-yl)-*N*, *N*, *N'*, *N'*-tetramethyluronium hexafluorophosphate (317mg, 0.83mmol) and *N*,*N*-dimethylglycine (86mg, 0.83mmol) were dissolved in *N*,*N*-dimethylformamide (10ml) and diisopropylethylamine (0.24ml, 1.39mmol) was added. The reaction mixture was stirred at room temperature over night, diluted with ethyl acetate, washed with brine (x2), 2N sodium hydroxide, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue (3% 7N ammonia in methanol/dichloromethane) gave **4-(4-bromo-2-fluoroanilino)-7-(2-{1-[(*N*,*N*-dimethylamino)acetyl]piperidin-4-yl}ethoxy)-6-methoxyquinazoline** (330mg, 85%) as a white solid.

LC-MS (ESI) 562.1 [M(^{81}Br)H]$^+$

^{1}H NMR (spectrum): (DMSOd$_6$) 1.03-1.19 (m, 2H); 1.76 (m, 5H); 2.18 (s, 6H); 5.56 (br t, 1H); 2.98 (m, 2H); 3.11 (br d, 1H); 3.95 (s, 3H); 4.03 (br d, 1H); 4.20 (m, 2H); 4.34 (br d, 1H); 7.22 (s, 1H); 7.47 (dd, 1H); 7.54 (t, 1H); 7.65 (dd, 1H); 7.79 (s, 1H); 8.36 (s, 1H); 9.50 (s, 1H)

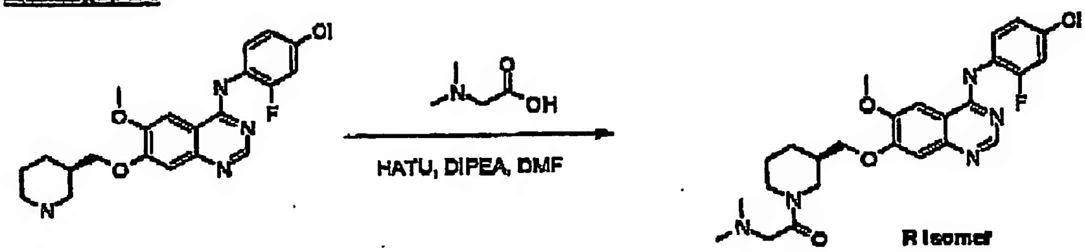
The starting material was prepared as follows:

tert-Butyl 4-{2-[(4-chloro-6-methoxyquinazolin-7-yl)oxy]ethyl}piperidine-1-carboxylate (0.4g, 0.95mmol), (prepared as described for the starting material in Example 12), and 4-bromo-2-fluoroaniline (216mg, 1.14mmol) were stirred in 2-propanol (15ml) and hydrogen chloride (1.2ml of a 4M solution in dioxane, 4.75mmol) was added. The mixture was heated at reflux for 1.5 hours, cooled and concentrated under reduced pressure. Column chromatography of the residue (10% 7N ammonia in methanol/dichloromethane) gave 4(4-bromo-2-fluoroanilino)-6-methoxy-7-[2-(piperidin-4-yl)ethoxy]quinazoline (339mg, 75%) as a white solid.

LC-MS (ESI) 472.9 and 474.9 [M-H]$^-$

^{1}H NMR (spectrum): (DMSOd$_6$) 1.10 (m, 2H); 1.58 (m, 1H); 1.69 (m, 4H); 2.46 (dt, 2H); 2.92 (br d, 2H); 3.94 (s, 3H); 4.18 (t, 2H); 7.20 (s, 1H); 7.46 (m, 1H); 7.53 (t, 1H); 7.59 (dd, 1H); 7.79 (s, 1H); 8.35 (s, 1H), 9.51 (br s, 1H)

Example 14



4-(4-Chloro-2-fluoroanilino)-6-methoxy-7-[(3*R*)-piperidin-3-ylmethoxy]quinazoline (150mg, 0.36mmol), *O*-(7-azabenzotriazol-1-yl)-*N*, *N*, *N'*, *N'*-tetramethyluronium hexafluorophosphate (164mg, 0.43mmol) and *N,N*-dimethylglycine (45mg, 0.43mmol) were dissolved in *N,N*-dimethylformamide (4ml) and diisopropylethylamine (0.125µl, 0.72mmol) was added. The reaction mixture was stirred at room temperature for 2 hours, diluted with ethyl acetate, washed with brine (x2), 2N sodium hydroxide, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue (2.5% 7N ammonia in methanol/dichloromethane) gave **4-(4-chloro-2-fluoroanilino)-7-({(3*R*)-1-[(*N,N*-dimethylamino)acetyl]piperidin-3-yl}methoxy)-6-methoxyquinazoline** (138mg, 76%) as a white solid.

LC-MS (ESI) 502 and 504 $[MH]^+$

^1H NMR (spectrum): (DMSOd_6 at 373°K) 1.45 (m, 2H); 1.71 (m, 1H); 1.91 (m, 1H); 2.08 (m, 1H); 2.21 (s, 6H); 3.05 (m, 4H); 3.95 (m, 4H); 4.10 (m, 2H); 4.20 (m, 1H); 7.21 (s, 1H); 7.30 (d, 1H); 7.40 (d, 1H); 7.65 (t, 1H); 7.80 (s, 1H); 8.37 (s, 1H); 9.15 (s, 1H)

The starting material was prepared as follows:

4-Chloro-7-hydroxy-6-methoxyquinazoline (250mg, 1.19mmol), (prepared as described for the starting material in Example 1), *tert*-butyl (3*R*)-3-(hydroxymethyl)piperidine-1-carboxylate (307mg, 1.42mmol) and triphenylphosphine (374mg, 1.42mmol) were stirred in dichloromethane (12ml) and cooled in an ice/water bath. Diisopropyl azodicarboxylate (280µl, 1.42mmol) in dichloromethane (2ml) was slowly added and the mixture stirred at room temperature for 2.5 hours before being concentrated under reduced pressure. Column chromatography of the residue (2:1 isohexane/ethyl acetate) gave *tert*-butyl (3*R*)-3-{[(4-chloro-6-methoxyquinazolin-7-yl)oxy]methyl}piperidine-1-carboxylate (400mg, 82%) as a viscous oil.

LC-MS (ESI) 408 and 410 $[MH]^+$

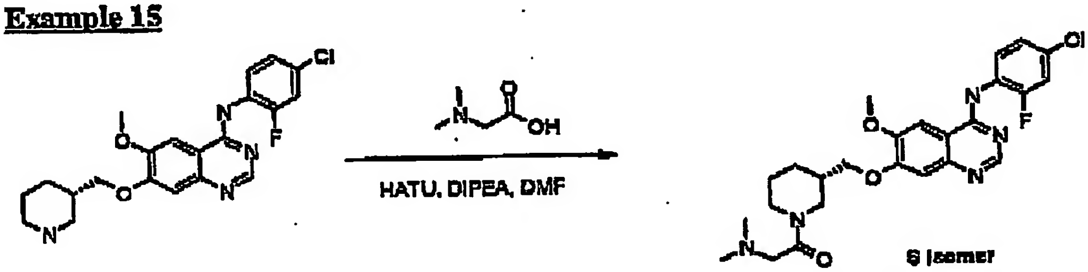
^1H NMR (spectrum): (DMSOd_6) 1.36 (m, 11H); 1.60 (m, 1H); 1.87 (m, 1H); 1.99 (m, 1H); 2.90 (m, 1H); 3.72 (m, 1H); 4.01 (m, 7H); 7.40 (s, 1H); 7.46 (s, 1H); 8.87 (s, 1H)

tert-Butyl (3*R*)-3-{[(4-chloro-6-methoxyquinazolin-7-yl)oxy]methyl}piperidine-1-carboxylate (400mg, 0.98mmol) and 4-chloro-2-fluoroaniline (130µl, 1.18mmol) were stirred in 2-propanol (12ml) and hydrogen chloride (294µl of a 4M solution in dioxane, 1.18mmol) was added. The mixture was heated at reflux for 4 hours, cooled and filtered. The solid was dissolved in methanol, absorbed onto an Isolute® column, washed with methanol and eluted with 7N ammonia in methanol to give 164mg of first batch of product as a white solid. Column chromatography of the concentrated filtrate (10% 7N ammonia in methanol/dichloromethane) gave a further 41mg of 4-(4-chloro-2-fluoroanilino)-6-methoxy-7-[(3*R*)-piperidin-3-ylmethoxy]quinazoline which was combined with the first batch (205mg in total, 50%).

LC-MS (ESI) 417 and 419 $[MH]^+$

^{1}H NMR (spectrum): (DMSOd_6) 1.25 (m, 1H); 1.41 (m, 1H); 1.59 (m, 1H); 1.84 (m, 1H); 1.95 (m, 1H); 2.38 (t, 1H); 2.50 (m, 1H); 2.86 (d, 1H); 3.07 (d, 1H); 3.95 (s, 3H); 4.00 (d, 2H); 7.18 (s, 1H); 7.34 (d, 1H); 7.54 (dd, 1H); 7.59 (t, 1H); 7.79 (s, 1H); 8.35 (s, 1H); 9.51 (s, 1H)

Example 15



4-(4-Chloro-2-fluoroanilino)-7-({(3*S*)-1-[(*N*,*N*-dimethylamino)acetyl]piperidin-3-yl}methoxy)-6-methoxyquinazoline was prepared using an analogous procedure to that described in Example 14.

LC-MS (ESI) 502 and 504 $[MH]^+$

^{1}H NMR (spectrum): (DMSOd_6 at 373°K) 1.45 (m, 2H); 1.71 (m, 1H); 1.91 (m, 1H); 2.08 (m, 1H); 2.21 (s, 6H); 3.05 (m, 4H); 3.95 (m, 4H); 4.10 (m, 2H); 4.20 (m, 1H); 7.21 (s, 1H); 7.30 (d, 1H); 7.40 (d, 1H); 7.65 (t, 1H); 7.80 (s, 1H); 8.37 (s, 1H); 9.15 (s, 1H)

The starting material was prepared as follows:

4-Chloro-7-hydroxy-6-methoxyquinazoline was reacted with (3*S*)-3-(hydroxymethyl)piperidine-1-carboxylate using an analogous procedure to that described for

the starting material in Example 14 to give *tert*-butyl (3*S*)-3-{[(4-chloro-6-methoxyquinazolin-7-yl)oxy]methyl}piperidine-1-carboxylate

LC-MS (ESI) 408 and 410 $[MH]^+$

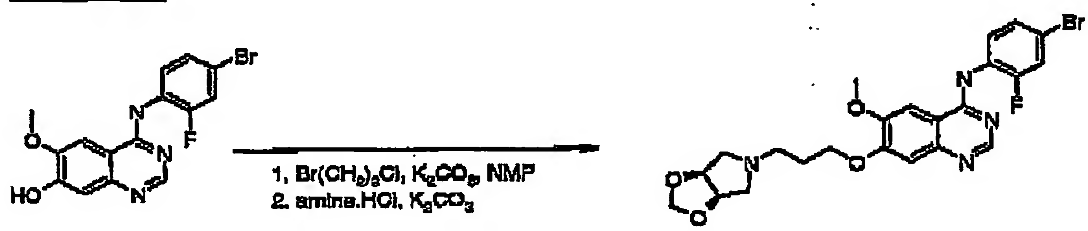
^{1}H NMR (spectrum): ($DMSOd_6$) 1.36 (m, 11H); 1.60 (m, 1H); 1.87 (m, 1H); 1.99 (m, 1H); 2.90 (m, 1H); 3.72 (m, 1H); 4.01 (m, 7H); 7.40 (s, 1H); 7.46 (s, 1H); 8.87 (s, 1H)

4-(4-Chloro-2-fluoroanilino)-6-methoxy-7-[(3*S*)-piperidin-3-ylmethoxy]quinazoline was prepared using an analogous procedure to that described for the starting material in Example 14.

LC-MS (ESI) 417 and 419 $[MH]^+$

^{1}H NMR (spectrum): ($DMSOd_6$) 1.25 (m, 1H); 1.41 (m, 1H); 1.59 (m, 1H); 1.84 (m, 1H); 1.95 (m, 1H); 2.38 (t, 1H); 2.50 (m, 1H); 2.86 (d, 1H); 3.07 (d, 1H); 3.95 (s, 3H); 4.00 (d, 2H); 7.18 (s, 1H); 7.34 (d, 1H); 7.54 (dd, 1H); 7.59 (t, 1H); 7.79 (s, 1H); 8.35 (s, 1H); 9.51 (s, 1H)

<u>**Example 16**</u>



4-(4-Bromo-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (986mg, 2.71mmol) and potassium carbonate (412mg, 2.98mmol) were stirred in 1-methylpyrrolidinone (10ml) and 1-bromo-3-chloropropane (295µl, 2.98mmol) added. The mixture was stirred at 90°C for 2 hours. (3a*R*,6a*S*)-Tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]pyrrole hydrochloride (452mg, 2.98mmol), (prepared as described for the starting material in Example 6), potassium carbonate (412mg, 2.98mmol) and a catalytic amount of potassium iodide were added and the mixture heated at 90°C for a further 3 hours. The mixture was cooled and partitioned between water and dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated and the residue purified by a combination of column chromatography (1% 1N ammonia in methanol/dichloromethane) and preparative HPLC to give **4-(4-bromo-2-fluoroanilino-6-methoxy-7-{3-[(3a*R*,6a*S*)-tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-yl]propoxy}quinazoline** (276mg, 23%) as a white solid.

LC-MS (ESI) 520.9 $[M(^{81}Br)H]^+$

^{1}H NMR (spectrum): (DMSOd$_6$) 1.95 (m, 2H); 2.15 (brd, 2H); 2.42 (m, 2H); 3.01 (d, 2H); 3.95 (s, 3H); 4.17 (t, 2H); 4.57 (m, 2H); 4.86 (s, 1H); 4.95 (s, 1H); 7.17 (s, 1H); 7.47 (m, 1H); 7.54 (t, 1H); 7.65 (dd, 1H); 7.80 (s, 1H); 8.36 (s, 1H); 9.51 (s, 1H).

The starting material was prepared as follows:

A mixture of 2-amino-4-benzyloxy-5-methoxybenzamide (J. Med. Chem. 1977, vol 20, 146-149, 10g, 0.04mol) and Gold's reagent (7.4g, 0.05mol) in dioxane (100ml) was stirred and heated at reflux for 24 hours. Sodium acetate (3.02g, 0.037mol) and acetic acid (1.65ml, 0.029mol) were added to the reaction mixture and it was heated for a further 3 hours. The mixture was evaporated, water was added to the residue, the solid was filtered off, washed with water and dried ($MgSO_4$). Recrystallisation from acetic acid gave 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.7g, 84%).

A mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (2.82g, 0.01mol), thionyl chloride (40ml) and DMF (0.28ml) was stirred and heated to reflux for 1 hour. The mixture was evaporated, the residue was taken up in toluene and evaporated to dryness to give 7-benzyloxy-4-chloro-6-methoxyquinazoline (3.45g).

A solution of 7-benzyloxy-4-chloro-6-methoxyquinazoline (8.35g, 27.8mmol) and 4-bromo-2-fluoroaniline (5.65g, 29.7mmol) in 2-propanol (200ml) was heated at reflux for 4 hours. The resulting precipitate was collected by filtration, washed with 2-propanol and then ether and dried under vacuum to give 7-benzyloxy-4-(4-bromo-2-fluoroanilino)-6-methoxyquinazoline hydrochloride (9.46g, 78%).

^{1}H NMR Spectrum: (DMSOd$_6$; CD_3COOD) 4.0(s, 3H); 5.37(s, 2H); 7.35-7.5(m, 4H); 7.52-7.62(m, 4H); 7.8(d, 1H); 8.14(9s, 1H); 8.79(s, 1H)

MS - ESI: 456 [MH]$^+$

Elemental analysis:	Found	C 54.0	H 3.7	N 8.7
$C_{22}H_{17}N_3O_2BrF$ 0.9HCl	Requires	C 54.2	H 3.7	N 8.6%

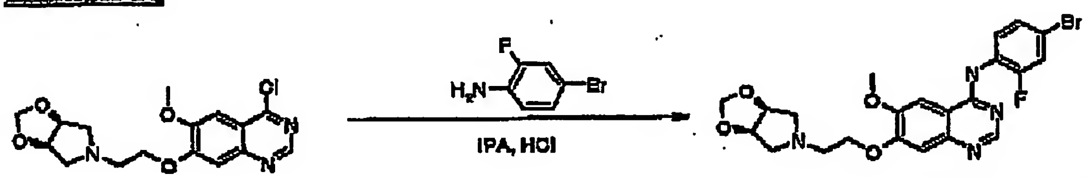
A solution of 7-benzyloxy-4-(4-bromo-2-fluoroanilino)-6-methoxyquinazoline hydrochloride (9.4g, 19.1mmol) in TFA (90ml) was heated at reflux for 50 minutes. The mixture was allowed to cool and was poured on to ice. The resulting precipitate was collected by filtration and dissolved in methanol (70ml). The solution was adjusted to pH9-10 with concentrated aqueous ammonia solution. The mixture was concentrated to half initial volume by evaporation. The resulting precipitate was collected by filtration, washed with water and then ether, and dried under vacuum to give 4-(4-bromo-2-fluoroanilino)-7-hydroxy-6-methoxyquinazoline (5.66g, 82%).

^{1}H NMR Spectrum: (DMSOd$_6$; CD$_3$COOD) 3.95(s, 3H); 7.09(s, 1H); 7.48(s, 1H); 7.54(t, 1H); 7.64(d, 1H); 7.79(s, 1H); 8.31(s, 1H)

MS - ESI: 366 [MH]$^+$

Elemental analysis:	Found	C 49.5	H 3.1	N 11.3
$C_{15}H_{11}N_3O_2BrF$	Requires	C 49.5	H 3.0	N 11.5%

Example 17



4-Chloro-6-methoxy-7-{2-[(3a*R*,6a*S*)-tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-yl]ethoxy}quinazoline (270mg, 0.77mmol) was suspended in 2-propanol (10ml) and 4-bromo-2-fluoroaniline (175mg, 0.92mmol) added. Hydrogen chloride (230µl of a 4M solution in dioxane, 0.92mmol) was added and the mixture heated at reflux for 1.5 hours, cooled and the solid filtered off. The solid was dissolved in 7M ammonia in methanol, concentrated under reduced pressure, water added and the solid filtered off and dried to give **4-(4-bromo-2-fluoroanilino)-6-methoxy-7-{2-[(3a*R*,6a*S*)-tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-yl]ethoxy}quinazoline** (295mg, 76%) as a white solid.

LC-MS (ESI) 506.9 [M(^{81}Br)H]$^+$

^{1}H NMR (spectrum): (DMSOd$_6$) 2.28 (br d, 2H); 2.80 (t, 2H); 3.12 (d, 2H); 3.95 (s, 3H); 4.24 (t, 2H); 4.56 (m, 2H); 4.82 (s, 1H); 4.97 (s, 1H); 7.23 (s, 1H); 7.47 (m, 1H); 7.54 (t, 1H); 7.65 (dd, 1H); 7.80 (s, 1H); 8.36 (s, 1H); 9.51 (s, 1H)

The starting material was prepared as follows:

(3a*R*,6a*S*)-Tetrahydro-3a*H*-[1,3]dioxolo[4,5-c]pyrrole hydrochloride (0.7g, 4.62mmol), (prepared as described for the starting material in Example 6), potassium carbonate (1.6g, 11.5mmol) and 2-bromoethanol (0.33ml, 4.62mmol) were heated in acetonitrile (30ml) at reflux for 2 hours. The mixture was cooled, filtered and concentrated under reduced pressure. Column chromatography of the residue (5% methanol/dichloromethane) gave a pale orange oil which was dissolved in methanol, absorbed onto an Isolute® SCX column, washed with methanol and eluted with 7N ammonia in methanol to give 2-[(3a*R*,6a*S*)-tetrahydro-5*H*-[1,3]dioxolo[4,5-c]pyrrol-5-yl]ethanol (313mg, 43%) as a pale yellow oil.

^{1}H NMR (spectrum): ($CDCl_3$) 2.29 (m, 3H); 2.59 (t, 2H); 3.17 (d, 2H); 3.63 (t, 2H); 4.60 (m, 2H); 4.92 (s, 1H); 5.09 (s, 1H)

4-Chloro-7-hydroxy-6-methoxyquinazoline (330mg, 1.57mmol), (prepared as described for the starting material in Example 1), 2-[(3a*R*,6a*S*)-tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-yl]ethanol (300mg, 1.88mmol) and triphenylphosphine (494mg, 1.88mmol) were stirred in dichloromethane (10ml) and cooled in an ice/water bath. Diisopropyl azodicarboxylate (371μl, 1.88mmol) in dichloromethane (2ml) was slowly added and the mixture stirred at room temperature for 3 hours before being concentrated under reduced pressure. Column chromatography of the residue (1%-2% methanol/dichloromethane) gave 4-chloro-6-methoxy-7-{2-[(3a*R*,6a*S*)-tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-yl]ethoxy}quinazoline (280mg, 51%) as a white solid.

LC-MS (ESI) 352 and 354 [MH]$^+$

^{1}H NMR (spectrum): (DMSOd_6) 2.28 (d, 2H); 2.82 (t, 2H); 3.12 (d, 2H); 4.01 (s, 3H); 4.33 (t, 2H); 4.56 (m, 2H); 4.81 (s, 1H); 4.96 (s, 1H); 7.41 (s, 1H); 7.50 (s, 1H); 8.88 (s, 1H)

<u>Example 18</u>

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)	<u>Tablet I</u>	<u>mg/tablet</u>
	Compound X	100
	Lactose Ph.Eur	182.75
	Croscarmellose sodium	12.0
	Maize starch paste (5% w/v paste)	2.25
	Magnesium stearate	3.0

(b)	<u>Tablet II</u>	<u>mg/tablet</u>
	Compound X	50
	Lactose Ph.Eur	223.75
	Croscarmellose sodium	6.0
	Maize starch	15.0
	Polyvinylpyrrolidone (5% w/v paste)	2.25

	Magnesium stearate	3.0
(c)	Tablet III	mg/tablet
	Compound X	1.0
	Lactose Ph.Eur	93.25
	Croscarmellose sodium	4.0
	Maize starch paste (5% w/v paste)	0.75
	Magnesium stearate	1.0
(d)	Capsule	mg/capsule
	Compound X	10
	Lactose Ph.Eur	488.5
	Magnesium stearate	1.5
(e)	Injection I	(50 mg/ml)
	Compound X	5.0% w/v
	1M Sodium hydroxide solution	15.0% v/v
	0.1M Hydrochloric acid (to adjust pH to 7.6)	
	Polyethylene glycol 400	4.5% w/v
	Water for injection to 100%	
(f)	Injection II	10 mg/ml)
	Compound X	1.0% w/v
	Sodium phosphate BP	3.6% w/v
	0.1M Sodium hydroxide solution	15.0% v/v
	Water for injection to 100%	
(g)	Injection III	(1mg/ml,buffered to pH6)
	Compound X	0.1% w/v
	Sodium phosphate BP	2.26% w/v
	Citric acid	0.38% w/v
	Polyethylene glycol 400	3.5% w/v

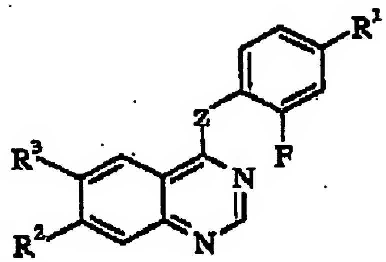
Water for injection to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CLAIM

1. A compound of the formula I:



(I)

wherein:

Z is -NH-, -O- or -S-;

R^1 represents bromo or chloro;

R^3 represents C_{1-3}alkoxy or hydrogen;

R^2 is selected from one of the following three groups:

(i) Q^1X^1-

wherein X^1 represents -O-,-S- or -NR^4- wherein R^4 is hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl and Q^1 is selected from one of the following ten groups:

1) Q^2 (wherein Q^2 is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which heterocyclic group may optionally bear a further 1 or 2 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy

and a group -(-O-)$_f$($C_{1\text{-}4}$alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from $C_{1\text{-}4}$alkyl), or Q^2 bears a single substituent selected from methylenedioxy and ethylenedioxy); with the proviso that if Q^1 is Q^2 and X^1 is -O- then Q^2 must bear at least one substituent selected from $C_{2\text{-}5}$alkenyl, $C_{2\text{-}5}$alkynyl, $C_{1\text{-}4}$alkoxy$C_{1\text{-}4}$alkylamino$C_{2\text{-}6}$alkanoyl, carbamoyl$C_{1\text{-}6}$alkyl, $C_{1\text{-}4}$alkylcarbamoyl$C_{1\text{-}6}$alkyl, and di($C_{1\text{-}4}$alkyl)carbamoyl$C_{1\text{-}6}$alkyl and optionally may bear a further 1 or 2 substituents as defined hereinbefore;

2) $C_{1\text{-}5}$alkylW^1Q^2 (wherein W^1 represents -O-, -S-, -SO-, -SO_2-, -C(O)-, -OC(O)-, -NQ^3C(O)-, -C(O)NQ^4-, -SO_2NQ^5-, -NQ^6SO_2- or –NQ^7- (wherein Q^3, Q^4, Q^5, Q^6 and Q^7 each independently represents hydrogen, $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$alkoxy$C_{2\text{-}3}$alkyl, $C_{2\text{-}5}$alkenyl, $C_{2\text{-}5}$alkynyl or $C_{1\text{-}4}$haloalkyl) and Q^2 is as defined hereinbefore;

3) $C_{1\text{-}5}$alkylQ^2 (wherein Q^2 is as defined hereinbefore);

4) $C_{2\text{-}5}$alkenylQ^2 (wherein Q^2 is as defined hereinbefore);

5) $C_{2\text{-}5}$alkynylQ^2 (wherein Q^2 is as defined hereinbefore);

6) $C_{1\text{-}4}$alkyl$W^2C_{1\text{-}4}$alkylQ^2 (wherein W^2 represents -O-, -S-, -SO-, -SO_2-, -C(O)-, -OC(O)- -NQ^8C(O)-, -C(O)NQ^9-, -SO_2NQ^{10}-, -$NQ^{11}SO_2$- or –NQ^{12}- (wherein Q^8, Q^9, Q^{10}, Q^{11} and Q^{12} each independently represents hydrogen, $C_{1\text{-}3}$alkyl, $C_{1\text{-}3}$alkoxy$C_{2\text{-}3}$alkyl, $C_{2\text{-}5}$alkenyl, $C_{2\text{-}5}$alkynyl or $C_{1\text{-}4}$haloalkyl) and Q^2 is as defined hereinbefore);

7) $C_{2\text{-}5}$alkenyl$W^2C_{1\text{-}4}$alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

8) $C_{2\text{-}5}$alkynyl$W^2C_{1\text{-}4}$alkylQ^2 (wherein W^2 and Q^2 are as defined hereinbefore);

9) $C_{1\text{-}4}$alkylQ^{13}($C_{1\text{-}4}$alkyl)$_j$(W^2)$_k$$Q^{14}$ (wherein W^2 is as defined hereinbefore, j is 0 or 1, k is 0 or 1, and Q^{13} and Q^{14} are each independently selected from hydrogen, $C_{1\text{-}3}$alkyl, cyclopentyl, cyclohexyl and a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which $C_{1\text{-}3}$alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and $C_{1\text{-}4}$alkoxy and which cyclic group may bear 1, 2 or 3 substituents selected from $C_{2\text{-}5}$alkenyl, $C_{2\text{-}5}$alkynyl, $C_{1\text{-}6}$fluoroalkyl, $C_{1\text{-}6}$alkanoyl, amino$C_{2\text{-}6}$alkanoyl, $C_{1\text{-}4}$alkylamino$C_{2\text{-}6}$alkanoyl, di($C_{1\text{-}4}$alkyl)amino$C_{2\text{-}6}$alkanoyl, $C_{1\text{-}4}$alkoxy$C_{1\text{-}4}$alkylamino$C_{2\text{-}6}$alkanoyl, $C_{1\text{-}6}$fluoroalkanoyl, carbamoyl, $C_{1\text{-}4}$alkylcarbamoyl, di($C_{1\text{-}4}$alkyl)carbamoyl, carbamoyl$C_{1\text{-}6}$alkyl, $C_{1\text{-}4}$alkylcarbamoyl$C_{1\text{-}6}$alkyl, di($C_{1\text{-}4}$alkyl)carbamoyl$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkylsulphonyl, $C_{1\text{-}6}$fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, $C_{1\text{-}4}$cyanoalkyl, $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$hydroxyalkyl, $C_{1\text{-}4}$alkoxy, $C_{1\text{-}4}$alkoxy$C_{1\text{-}}$

$_4$alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or more substituents selected from C_{1-4}alkyl), with the provisos that Q^{13} cannot be hydrogen and one or both of Q^{13} and Q^{14} must be a 5-6-membered saturated or partially unsaturated heterocyclic group as defined hereinbefore which heterocyclic group bears at least one substituent selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl and C_{1-6}fluoroalkylsulphonyl and which heterocyclic group optionally bears 1 or 2 further substituents selected from those defined hereinbefore); and

10) C_{1-4}alkylQ^{13}-C(O)-C_{1-4}alkylQ^{14a} wherein Q^{13} is as defined hereinbefore and is not hydrogen and Q^{14a} is a 5-6-membered saturated or partially unsaturated heterocyclic group containing at least one nitrogen atom and optionally containing a further heteroatom selected from N and O wherein Q^{14a} is linked to C_{1-6}alkyl via a nitrogen atom or a carbon atom and wherein Q^{14a} optionally bears 1, 2 or 3 substituents selected from C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-6}fluoroalkyl, C_{1-6}alkanoyl, aminoC_{2-6}alkanoyl, C_{1-4}alkylaminoC_{2-6}alkanoyl, di(C_{1-4}alkyl)aminoC_{2-6}alkanoyl, C_{1-4}alkoxyC_{1-4}alkylaminoC_{2-6}alkanoyl, C_{1-6}fluoroalkanoyl, carbamoyl, C_{1-4}alkylcarbamoyl, di(C_{1-4}alkyl)carbamoyl, carbamoylC_{1-6}alkyl, C_{1-4}alkylcarbamoylC_{1-6}alkyl, di(C_{1-4}alkyl)carbamoylC_{1-6}alkyl, C_{1-6}alkylsulphonyl, C_{1-6}fluoroalkylsulphonyl, oxo, hydroxy, halogeno, cyano, C_{1-4}cyanoalkyl, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkylsulphonylC_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, C_{1-4}alkylaminoC_{1-4}alkoxy, di(C_{1-4}alkyl)aminoC_{1-4}alkoxy and a group -(-O-)$_f$(C_{1-4}alkyl)$_g$ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 5-6-membered saturated or partially unsaturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear one or more substituents selected from C_{1-4}alkyl)

or Q^{14a} bears a single substituent selected from methylenedioxy and ethylenedioxy);

(ii) $Q^{15}W^{3}$-

wherein W^3 represents $-NQ^{16}C(O)-$, $-C(O)NQ^{17}-$, $-SO_2NQ^{18}-$, $-NQ^{19}SO_2-$ or $-NQ^{20}-$ (wherein Q^{16}, Q^{17}, Q^{18}, Q^{19} and Q^{20} each independently represents C_{2-5}alkenyl, C_{2-5}alkynyl, C_{1-4}haloalkyl), and Q^{15} is C_{1-6}haloalkyl, C_{2-5}alkenyl or C_{2-5}alkynyl; and

(iii) $Q^{21}W^{4}C_{1-5}$alkylX^1 wherein X^1 is as defined hereinbefore, W^4 represents $-NQ^{22}C(O)-$, $-C(O)NQ^{23}-$, $-SO_2NQ^{24}-$, $-NQ^{25}SO_2-$ or $-NQ^{26}-$ (wherein Q^{22}, Q^{23}, Q^{24}, Q^{25} and Q^{26} each independently represents hydrogen, C_{1-3}alkyl, C_{1-3}alkoxyC_{2-3}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl or C_{1-4}haloalkyl), and Q^{21} represents C_{1-6}haloalkyl, C_{2-5}alkenyl or C_{2-5}alkynyl;

or a salt thereof or a prodrug thereof.

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